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Clinical profile and outcome of the atypical manifestations of dengue fever at a teaching hospital in North India

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Abstract
Dengue is the most common Arboviral infection in the Southeast Asia. Clinically dengue infection varies from asymptomatic infection or mild fever to severe Dengue manifestations. The aim of the study was to investigate the clinical symptoms, laboratory findings and mortality in severe dengue at a medical college hospital. In this hospital based, retrospective study, we analyzed records of all the admitted patients between July 2019 to October 2019 diagnosed to have dengue who were serologically confirmed. In this retrospective study, 256 patients were included. There were 179(70%) patients in non-severe dengue group and 77(30%) in severe dengue group. Elevated liver enzymes were observed in 230(90%) patients and 213(83%) patients had thrombocytopenia. Various atypical manifestations in patients with severe dengue were recorded. The atypical manifestations of dengue fever are no more a rare entity. Early recognition, monitoring and administration of supportive care reduce morbidity and mortality.

Keywords: dengue, severe dengue, atypical manifestations, transaminitis, hypokalaemic paralysis

1. Introduction
Dengue is the most common arboviral infection in the Southeast Asia. Dengue virus has four related but antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 [1]. The global burden of dengue has increased in recent decades causing huge impact on human health. Clinically dengue infection varies from asymptomatic infection or mild fever to severe Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [2]. Although the disease with clinical features similar to dengue has been reported in India since 19th century but Dengue virus was first isolated and reported in India in1945 [3]. Thereafter there have been many outbreaks of dengue with increased cases of DHF and DSS [4]. Dengue is now an endemic disease in India especially in urban populations. A large number of dengue cases are reported every year in the months between July to December, with a peak in mid-September to mid-October [6]
Infection with any one serotype confers lifelong immunity to that virus serotype and only partial cross immunity to other serotypes. However, secondary infection with another serotype or multiple infections with different serotypes can lead to a severe form of disease[7] Although, vascular plasma leak is the commonest manifestation, dengue can manifest in multitude of unusual presentations due to organ dysfunction that can carry high mortality [8]. Early detection of such manifestations and prompt action could avert the adverse outcome where clinicians need knowledge and experience. The aim of the study was to investigate the clinical symptoms, laboratory findings and mortality in severe dengue at a medical college hospital.

2. Material and Methods
In this hospital based, retrospective study, we analyzed records of all the admitted patients between July 2019 to October 2019 diagnosed to have dengue who were serologically confirmed, by presence of either IgM or NS1. Patients were divided into dengue fever without warning signs, dengue with warning signs and severe dengue. Detailed history in form of demographic profile, symptoms, clinical examination and investigations were recorded. From all the case records clinical course of the illness, treatment given and outcome were noted.
According to the WHO's 2009 dengue case definition [9], dengue patients were classified into non-severe dengue and severe dengue based on clinical and laboratory criteria. Patients with non-severe dengue were subcategorized into two groups depending on the presence or absence of warning signs. Non-severe dengue without warning signs was defined as having acute fever with at least two of the following criteria: nausea, vomiting, rash, myalgia, arthralgia, a positive tourniquet test, or leukopenia. Warning signs included: (1) abdominal pain, (2) persistent vomiting (vomiting with signs of dehydration), (3) clinical fluid accumulation, (4) lethargy, (5) liver span >15 cm, (6) bleeding from mucosal areas including nose, gums, gastrointestinal tract or vagina, or (7) an elevated hematocrit, >2 % above the reference range for a healthy adult adjusted for gender with platelet counts $\leq 100\times10^3$ per μL.
Severe dengue was classified as having: (1) severe plasma leakage, defined as plasma leakage with shock or respiratory distress (respiratory rate ≥24 breaths/min with oxygen saturation <95 % in room air and/or requiring oxygen therapy), (2) severe clinical bleeding, defined as spontaneous bleeding from mucosal areas that necessitates a blood transfusion or bleeding in vital organs, (3) severe organ involvement, defined as AST >1000 IU/L and/or ALT >1000 IU/L, serum creatinine ≥3 times above baseline, myocarditis, and/or encephalitis.

3. Results

In this retrospective study, 256 patients were included. Out of them were 152 males and 104 females. The age range of the patients was 18 years to 62 years. The mean age was 34± 4 yrs. All the serologically confirmed patients were divided into two groups' non severe dengue and severe dengue, dengue fever without warning signs and dengue with warning signs constituted non-severe dengue. There were 179 (70%) patients in non-severe dengue group and 77(30%) in severe dengue group as shown in Table 1.

Analysis of clinical symptoms revealed that most common symptoms were fever, arthralgia, myalgia and anorexia followed by gastrointestinal manifestations. Among the different systems involvement, gastrointestinal symptoms were the commonest in form of nausea, vomiting and pain in abdomen. Elevated liver enzymes were observed in 230(90%) patients. The AST levels were much higher than ALT levels. Hepatomegaly, ascites, pleural effusion, acalculus cholecystitis were the type of affection. Two patients had high amylase and lipase so diagnosed to have acute pancreatitis and three patients had features of subacute intestinal obstruction. All of these patients were managed conservatively and discharged. Atypical manifestations have been shown in Table 2. Presence of petechiae, subconunctival hemorrhage, epistaxis and menorrhagia were the commonest hemorrhagic manifestations. Out of 256 patients, 213(83%) patients had thrombocytopenia. Eight patients had acute kidney injury at the time of admission who improved after appropriate fluid management.

Central nervous affection was observed in 6 patients. Out of these patients 3 had acute encephalitis, 2 had hypokalemic periodic paralysis and 1 had cerebral infarct. One patient had sinus tachycardia and raised troponin I and was diagnosed to have myocarditis. Two patients had DHF complicated with septic shock and multi-organ failure who needed mechanical ventilator assistance and renal replacement therapy but could not be salvaged.

Severity of dengue was positively correlated with delay in admission, raised hematocrit, elevated liver transaminases and signs of capillary leakage as depicted in Table 3.

4. Discussion

Dengue has become one of the fastest spreading diseases with half of the world population being at risk and millions of infections and taking thousands of lives every year [10]. In our hospital based retrospective analysis of admitted patient who were serologically positive for dengue found 77(30%) patients to have severe dengue which is similar to other studies. We also observed that most of the patients were young aged <40 years (70%) concordant with others.[11,12]

Most common system affected in our study was gastrointestinal tract and hepatobiliary system which is also reported by others [13, 14]. Hepatomegaly, ascites, and raised transaminases were most prevalent. Acalculus cholecystitis was found in 18% patients. Shaprio *et al*. showed that cholestasis, increased bile viscosity, and infection may be the causes [15]. Two of our patients had acute though mild pancreatitis as revealed by high amylase and lipase levels. Acute pancreatitis is a known complication of severe dengue [16].

Deranged hematological parameters in form of raised hematocrit and thrombocytopenia were present in 83% patients. Elevated hematocrit suggests a vasculopathy along with leakage, secondary to increasing vascular permeability. Recent studies have established hematocrit > 40% as a prognostic factor for severe dengue [8]. Additionally, in our study, hematocrit (≥40%) emerged as a strong independent predictor and it was positively correlated with severe dengue. Thrombocytopenia is one of the indicators of severe dengue but it was not correlated well in our study. The exact pathophysiology of thrombocytopenia in dengue is not yet clearly elucidated. Dengue virus may have a direct effect on the bone marrow -specially the progenitor cells causing a reduction in their capacity to replicate. There is also an increased consumption of platelets by disseminated intravascular coagulation [17].

We observed certain atypical manifestations of dengue infection in our study as reported in literature [18, 19]. Cardiovascular system involvement was seen 3 patients. One patient had myocarditis and 2 had pericardial effusion. Cardiac manifestations of dengue are uncommon but cardiac rhythm disorders such as atrio-ventricular blocks, atrial fibrillation and ectopic ventricular beats have been reportedly attributed to viral myocarditis [20, 21]. CNS was affected in 9 patients in heterogeneous way. Three patients diagnosed to have encephalitis without any focal neurological deficit normal brain imaging and cerebrospinal fluid (CSF) examination suggestive of viral meningitis and IgM positive dengue serology in CSF. They were treated conservatively and two of them improved. Another atypical presentation was hypokalemic paralysis, which was found in six patients who presented with acute onset quadriparesis and severe hypokalemia. They improved after correction of hypokalemia with intravenous potassium chloride infusion. Nerve conduction study, electromyography and imaging studies were normal in both the patients. Neurological manifestations like seizures, encephalopathy, encephalitis/aseptic meningitis, intracranial hemorrhages and neuropathies have been reported in the past [22, 23].

Acute kidney injury was the type of renal involvement in our study in which 8 patients had hypotension. They also had evidence of capillary leakage. They were treated conservatively and did not require renal replacement therapy. The present study noted delay in admission (≥5days onset) was significantly higher among the patients with severe dengue. Other factors which correlated with severity were rise in hematocrit, levels of transaminases and plasma leakage. The main pathophysiology of the capillary leak in dengue shock syndrome is due to compromised integrity of inter-endothelial cell junctional barrier. Ledika *et al*. [24] in his study noted a delay of more than 4 days of onset was significantly associated with severe dengue. Studies have established the mortality rate of 1-4% in severe dengue [25]. In our study, two patients expired who were admitted in intensive care unit with shock and multi-organ failure.

Our study has several limitations. It was a retrospective study which included patients from only a single center and our data may not be representative of dengue patients elsewhere secondly, only hospitalized patients were recruited to this study that included relatively less patients with non-severe dengue without warning signs.

5. Tables

Table 1: Patient characteristics and clinical parameters on admission

Parameter (%)	Non severe dengue (n=179)	Severe dengue(n=77)	P value
Hypotension(systolic blood pressure<90mmHg)	2(11%)	16(21%)	0.01
Bleeding manifestations	6(3%)	18(23%)	0.02
Signs of capillary leakage	0	61(79%)	0.001
Leucopenia (leucocyte count≤5000cells/mm3)	78(44%)	52(68%)	0.03
Thrombocytopenia (platelet count less than 1lac/mm3)	56(31%)	54(70%)	0.01

Table 2: Atypical manifestations recorded in study participants

GIT	Acalculus cholecystitis Acute pancreatitis
CVS	Myocarditis Pericardial effusion
CNS	Encephalitis convulsions Hypokalemic paralysis
Renal	Acute kidney injury
Pulmonary	Acute respiratory distress syndrome

Table 3: Correlation analysis with severity of dengue

Parameter	RHO	P value
Delay in admission(>5days)	0.72	0.001
Hematocrit (>40%)	0.56	0.01
Elevation of transaminase(>1000IU)	0.46	0.002
Presence of capillary leakage	0.48	0.01

6. Statistical analysis

Statistical analysis was performed using the SPSS software, Version 20. Total numbers and percentages were calculated for different categorical variables, such as clinical features and biochemical parameters. Spearman's correlation test was used to study correlation between severe dengue and other parameters and a p-value <0.05 was considered statistically significant.

7. Conclusions

Dengue is of significant public health importance as is evident from the evolution of the recent outbreaks spanning over more than a decade that has witnessed more severe disease and haemorrhagic manifestations. The atypical manifestations of dengue fever are no more a rare entity. There is an urgent need for prognostic assays to predict progression to severe dengue infection, which is a major global threat. Early monitoring and administration of supportive care reduce morbidity and mortality.

8. Source of support: Nil
9. Conflict of interest: None

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