Original Article:

Clinical, laboratory profile and outcome of dengue fever at a south Indian tertiary care hospital

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ABSTRACT

Background: Dengue fever is a rapidly spreading mosquito-borne viral disease in the world.

Methods: We prospectively studied adult patients with dengue fever (n=148) at our tertiary care teaching hospital from November 2010 to September 2012. Their clinical presentation, laboratory manifestation and outcome are reported.

Results: Eighty eight (59.1%) patients had severe forms of dengue fever. The various complaints noted by patients included vomitings, headache, body aches, low backache, retro-orbital pain, rash, loose motions, pain abdomen and jaundice. Melena was the most common bleeding manifestation. Thrombocytopenia was present in 91.9% of patients. Elevation of hepatic transaminases was found in 80.9% of patients. Hypoalbuminemia (serum albumin <3.5 g/dL) was present in 62 (42.9%) patients. Albuminuria was seen in 39 (26.4%) patients. Abdominal ultrasonography showed ascites in 28.6%, hepatomegaly in 26.1%, splenomegaly in 28.4%, and acalculous cholecystitis in 20.5%. Chest radiograph showed pleural effusion in 31(21%) patients. Electrocardiogram revealed bradycardia in 30 (20.3%) patients. Packed red cell transfusion was given to 14 (9.5%) patients and platelet rich plasma (PRP) and single donor platelets (SDP) were given to 36 (24.3%) patients with severe dengue fever. Of the 148 patients, nine (6.1%) died.

Conclusions: Fever, vomiting were the most common symptoms, melena was the most common bleeding manifestation in patients presenting with dengue fever.

Key words: *Dengue fever, Warning signs, India, Severe dengue*

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INTRODUCTION

Dengue fever (DF) is an acute febrile illness caused by dengue viruses (DEN-1 to 4) belonging to the family Flaviviridae. An estimated 50 million dengue infections occur annually, and approximately 2.5 billion people live in dengue endemic countries.[1] Several outbreaks of DF have been reported from India.[2,3,4] DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary DF.[5] Dengue viruses are transmitted to humans through the bite of infected *Aedes* mosquitoes, principally *Aedes aegypti*. Infectious virus and the virus-encoded NS1 are present in blood during the acute phase, and high level early viraemia and NS1 antigenaemia have been associated with more severe clinical presentations.[6] Dengue has become endemic in parts of the world due to rapid urbanization, with increased population density with an abundance of vector breeding sites.[7]

Clinical manifestations of DF are varied and can mislead the physician with the other common infections that are prevalent in the community, such as malaria, typhoid, leptospirosis, scrub typhus, community acquired pneumonia and enteroviral

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gastroenteritis. Patients with dengue fever may not have specific localizing symptoms at the time of presentation. It is important to diagnose the aetiological agent in acute pyrexia quickly to prevent complications like shock and bleeding in dengue fever and avoid unnecessary use of antibacterials agents. We describe the clinical, laboratory findings and outcome of serologically confirmed, hospitalized cases with DF in this paper.

MATERIAL AND METHODS

It is a prospective and observational study conducted between November 2010 to September 2012. We included all adult patients presenting with acute febrile illness with positive serological test for dengue antigen (NS1) or anti-dengue immunoglobulin M(Ig M) antibody. Patients with established infections, such as, malaria, enteric fever, bacterial sepsis, leptospirosis, chikungunya fever were excluded. Institutional Ethics Committee approval was taken before the initiation of study. Relevant history, clinical examination findings, laboratory data, and treatment details and outcome was collected from the patients after obtaining informed consent.

An immunchoromatographic (ICT) assay for rapid and simultaneous detection of Dengue NS1 antigen and Ig M and immunoglobulin G (Ig G) anti -dengue antibodies (SD Bio Line Dengue Duo, Standard Diagnostics, Korea) was used for initial screening of a patient clinically suspected with DF. All ICT positive specimen were confirmed using the Panbio® Dengue Duo IgM Capture and IgG Capture enzyme linked immunosorbent assay (ELISA) and NS1 antigen ELISA for a qualitative detection of IgM and IgG antibodies and NS1 antigen detection of the dengue virus.

Patients were categorized into three groups according to World Health Organization (WHO) newer grading system (2009)[1] as DF without warning signs, DF with warning signs and severe DF. DF without warning signs (Group 1) was defined as fever and presence of two of the following criteria: nausea/ vomiting, rash, aches and pains, leucopenia, positive tourniquet test. DF with warning signs (Group 2) was defined as patients with abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (ascites or pleural effusion), mucosal bleeding, lethargy or restlessness, liver enlargement (>2 cm), or an increase in haematocrit with concurrent rapid fall in platelet count. Severe DF (Group 3) included patients with plasma leakage leading to shock (dengue shock syndrome, DSS) or fluid accumulation with respiratory distress, severe bleeding (as evaluated by a clinician), and /or severe organ involvement [i.e., (AST) or alanine aminotransferase (ALT) 1000 or greater, impaired consciousness or organ failure]. Patients were managed as per 2009 WHO guidelines[1] according to severity grade.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and proportions for categorical variables.

RESULTS

Of the 148 patients included in the study, 85 (57.4%) were males; 73% were < 40 years of age. Fifteen (10.1%) 45 (30.4%), 88 (59.46%) had DF (Group 1), DF with warning signs (Group 2), severe DF (Group 3) grades respectively. There was no significant difference in the age distribution of these patients 32.8±15 years in males and 33.4±15 in females. There was significant seasonal distribution with nearly 95% admissions occurring in the second half of the year (July to December).

The clinical presentation (Table 1) included fever in all patients. Other symptoms were vomitings, headache, body pains, rash, loose stools, pain abdomen, jaundice, low back pain and retroorbital pain. Physical examination revealed rash, pallor, injected conjunctiva,

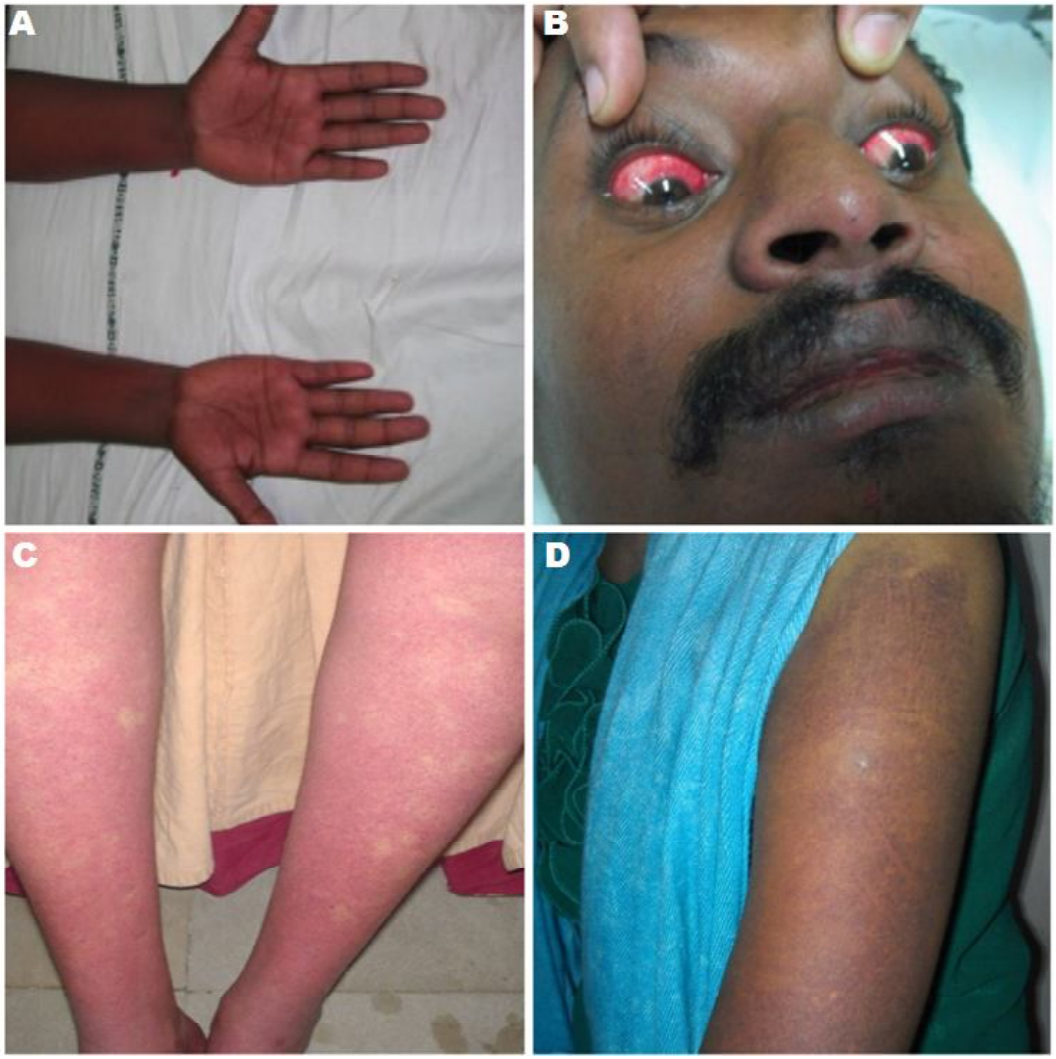

Figure 1: Clinical photograph showing erythematous rash **(A),** subconjunctival haemorrhage **(B),** skin rash with "white islands in a sea of red" appearance **(C),** Haematoma following intramuscular injection **(D)**

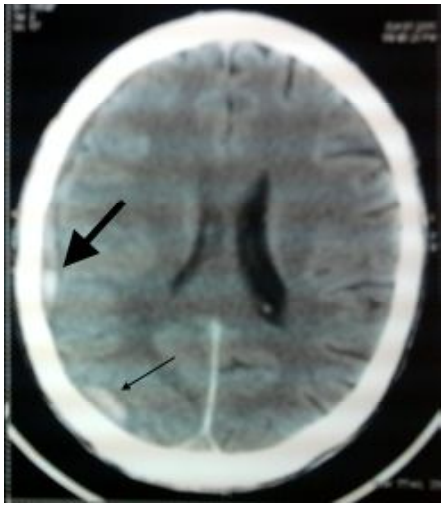

Figure 2: NCCT head in a patient with severe dengue fever showing subdural haematoma in night front-oparietal region (thick arrow), small epidural haemorrhage in posterior high parietal region (thin arrow). Hyperdense posterior falx suggests pontine haemorrhage

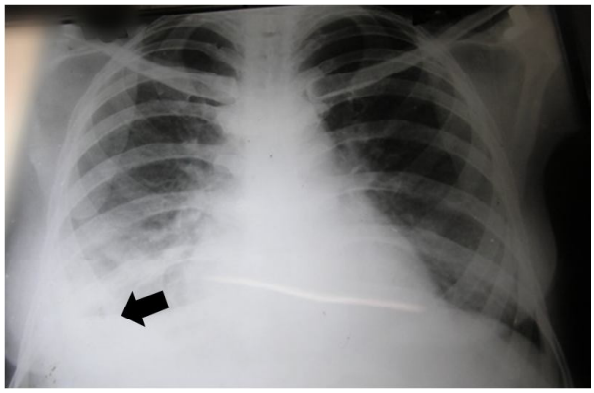

Figure 3: Chest radiograph (postero-anterior view) showing right-sided pleural effusion (arrow)

Table1: Presenting symptoms and signs

Variable	Total (n=148) No. (%) No.		DF without warning signs (n=15) No.	DF with warning signs (n=45) No.	Severe DF (n=88) No.
Symptoms					
Fever	148	(100)	15	45	88
Vomiting	54	(36.5)	6	12	36
Headache	33	(22.3)	4	9	20
Pain abdomen	30	(20.3)	0	10	20
Body pains	29	(19.6)	2	9	18
Rash	18	(12.2)	1	7	10
Loose stools	15	(10.1)	2	5	8
BackPain	2	(1.4)	0	0	2
Arthralgias	4	(2.7)	2	0	2
Jaundice	7	(4.7)	0	1	6
Retroorbital pain	2	(1.4)	0	0	2
Signs					
Rash	47	(31.7)	2	15	30
Pallor	37	(25.0)	2	6	29
Conjunctival congestion	13	(8.8)	2	4	7
Hepatomegaly	23	(15.6)	0	8	15
Splenomegaly	25	(16.9)	0	10	15

DF = dengue fever

hepatomegaly, splenomegaly (Table 1). Salient clinical manifestation are presented in Figures 1, 2 and 3. Haematological investigations are shown in Table 2. Gastrointestinal bleeding was the most common bleeding manifestation (Table 2). Neurological complications were seen in 9 (6%) of study patients which included acute demyelinating encephalomyelitis (ADEM), Guillain-Barre syndrome (GBS) and myelitis.

Elevation of hepatic transaminases was present in 105 (71%) of patients (Table 3A). Of these 105 patients with hepatitis, 85 (81%) patients had mild to moderate hepatitis (up to ten-fold elevation) whereas the remaining 20 (19.1%) had severe hepatitis (>10-fold elevation). Hypoalbuminemia (serum albumin <3.5 g/dL) was present in 62 (42.9%) patients. Urine examination showed albuminuria (>2+) in 39 (26.4%) and microscopic haematuria in 49 (33.1%) patients. Elevated serum creatinine was seen in 6 (4.1%) patients.

Ultrasonographic examination of abdomen performed in 95 patients (Table 3B), showed ascites in 29 (30.5%), hepatomegaly in 23 (24.2%), splenomegaly in 25 (26.3%), and acalculous cholecystitis in 18 (19%) patients.

Chest radiograph evidence of pleural effusion was found in 31 (21%) patients [13 (8.8%) DF with warning signs; and 18(12.2%) severe dengue]. None of the patients in the DF without warning signs had evidence of pleural effusion on chest radiographs. Chest radiograph with infiltrates suggestive of acute respiratory distress syndrome (ARDS) was found in patients with severe dengue. Electrocardiogram (ECG) revealed bradycardia in 30 (20.3%) patients all of whom had severe dengue.

NS1 antigen was detected in 80 (54.1%) patients. IgM antibody titres (≥1.2) were positive in 101 (68.2%) patients. IgG antibody titres (>2.0) were positive in 56 (37.8%).

Packed red cell transfusion was given to 14 (9.5%) patients all of whom had severe dengue. Platelet rich plasma (PRP) and single donor platelets (SDP) were given to 36 (24.3%)

Table 2A: Haematological abnormalities

Parameter	Total (n=148) No. (%)	DF without warning signs (n=15) No.	DF with warning signs (n=45) No.	Severe DF (n=88) No.
Haemoglobin*				
Males	13.5±2.6	13.19±2.6	13.9±2.6	13.2±2.7
Females	11.6±2.6	12.24±2.6	13.2±2.6	10.7±2.67
PCV*				
Males	40.7±8.1	38.83±8.1	40.9±8.1	40.8±8.2
Females	34.7±8.1	34.9±8.1	39.0 ±8.0	32.4±8.2
Total leucocyte count*	6915±5233	5800±5096	6447±5041	7337±5250
Leucopenia (<4000/mm^3) (No.)	51	7	13	31 (35)
Leucocytosis (>11000/mm^3) (No.)	22	2	2	18 (20)
Relative lymphocytosis (No.)	38	5	13	20 (22)
Atypical cells in peripheral smear (No.)	5	0	2	3 (2.03)
Thrombocytopenia				
Mild-to-moderate (30000/mm^3-100000/mm^3) (No.)	96	9	31(32.29) 10	56 (58.33)
Severe (<30000/mm^3) (No.)	40 (27.0)	4	10	26

* data are presented as mean ± standard deviation; DF = dengue fever

Table 2B : Bleeding complications

Complication	Total (n=148) No. (%)	DF without warning signs (n=15) No.	DF with warning signs (n=45) No.	Severe DF (n=88) No.
Melena	33 (22.3)	0	11	22
Haematemesis	4 (2.7)	0	1	3
Epistaxis	3 (2.0)	0	0	3
Gum bleeding	6 (4.1)	0	0	6
Haematuria	7 (4.7)	0	0	7
Haemoptysis	3 (2.1)	0	0	3
Increased menstrual flow	4 (2.7)	0	1	3
Intracranial bleeding	2 (1.4)	0	0	2

DF = dengue fever

Table 3A: Liver functions

Variable	Total (n=148) No. (%)	DF without warning signs (n=15) No.	DF with warning signs (n=45) No.	Severe DF (n=88) No.
Elevated bilirubin	17 (11.5)	0	6	11
Elevated ALP	47 (31.7)	0	12	35
Transaminitis (mild)	85 (57.4)	7	28	50
Transaminitis (severe)	20 (13.5)	0	1	19
Severe hypoalbuminemia(<2.5g/dL)	62 (41.9)	0	3	59

DF = dengue fever; ALP = alkaline phosphatase

Table 3B: Ultrasonographic findings

Observation	Total (n=95) No. (%)	DF without warning signs (n=15) No.	DF with warning signs (n=45) No.	Severe DF (n=88) No.
Ascites	29 (30.5)	0	9	20
Hepatomegaly	23 (24.2)	0	14	9
Splenomegaly	25 (26.3)	2	13	10
Gall bladder Oedema	18 (19.0)	1	3	14

DF = dengue fever

patients all with severe dengue. Fresh frozen plasma (FFP) was given to 8 (5.4%) patients, all with severe dengue.

Oral candidiasis was found in 23 (15.5%) patients and these were treated with topical clotrimazole lotion for application in the mouth. Antibiotics were initially administered to 39 (26.4%) patients, all with severe dengue. Mechanical ventilation was required in 9 patients with severe DF. Renal replacement therapy was required in nine patients. Nine patients died due to multiorgan failure.

DISCUSSION

Study of the clinical profile in DF is important for understanding the disease and patient management especially in the early part of illness to avoid complications. The 1997 WHO dengue classification scheme and case definitions were confusing and had drawbacks.[8,9] WHO revised the classification criteria in 2009, as DF without warning signs, DF with warning signs and severe DF. We managed our patients as per 2009 WHO guidelines according to severity grade. The primary management of patients with dengue includes fluid therapy either with oral rehydration solution or intravenous fluids depending on the severity.[1]

In our study 73% were patients aged <40 years, and male to female ratio was 1.8:1. This is possibly because young men go out doors for work, exposing themselves to mosquito bites as reported in other Indian studies.[10,11] Up to 95% were admitted in second half of each year (July to December) which is consistent with vector breeding season.[12]

Fever was a universal complaint followed by vomitings, loose motions, headache, and body pains. They may be confused with other febrile illnesses like viral gastroenteritis, typhoid and scrub typhus which are prevalent in our community. Loose stools were seen in 15 (11%) patients. Intestinal mucosal injury which may be responsible for loose motions in DF.[13]

Pain abdomen in DF is a warning sign and mandates admission and close monitoring. Causes of pain abdomen in DF include stretching of liver capsule due to hepatitis, pancreatitis, acalculous cholecystitis and peptic ulcer. Pain abdomen was found in 20.3% of our study population and similar findings have been reported in literature.[14,15] Higher incidence of pain abdomen up to 60% was noted in a study from Kerala.[11]

Physical examination plays an important role in the evaluation of a patient with DF. Hepatomegaly of more than 2 cm is a warning sign in severe grades of dengue according to WHO. Twenty three (15.5%) of our patients had hepatomegaly on clinical examination and all had severe DF. Presence of hepatomegaly is an important clue in the out-patient department to admit a patient with suspected dengue. Splenomegaly was seen in 25 (16.9%) patients on physical examination and similar numbers were reported in another study from India.[16]

Cutaneous manifestations are another important clue to the diagnosis of dengue fever. In patients with dengue infection, initially there is a transient flushing of face due to capillary dilatation. After 3-6 days of onset of fever, blanchable maculopapular rash associated with itching appears. Some patients develop haemorrhagic manifestations such as petechiae and ecchymoses, positive tourniquet test, particularly in severe dengue. In our study, an erythematous blanchable, itchy rash (Figure 1A) was observed in 47 (31.8%) patients. The rash was reported in 82% of cases in another study.[17] Lower incidence of rash in our patients could possibly difficulty in recognition due to dark skin colour. In some cases, individual lesions may coalesce and are seen as generalized confluent erythema with rounded islands of sparing (Figure 1C) described as "white islands in a sea of red".[18] WHO guidelines suggest that the intramuscular injections are contraindicated in patients with dengue infection. However, some of our patients presented with intramuscular haematoma (Figure 1D). This is because many of the clinicians did not diagnose the fever as DF and were not be aware of the patient's platelet count.

In our study, 62 (41.9%) patients developed bleeding manifestations, of which melena was the most common bleeding manifestation. Similar findings were reported in a study from Kerala.[11] Bleeding manifestations were seen in 37% patients in a large series from Brazil.[19] A higher proportion of bleeding manifestations were noted by Sharma et al.[14] Lum et al[20] described hypotension as a strong predictor of severe bleeding. Two patients in our study had serious bleeding manifestations in the form of subdural haematoma (SDH) (Figure 2) in one and intracerebral bleeding in another. A high index of suspicion is required in patients with DF during convalescence regarding intracranial bleed when they present with altered sensorium.[21] Increased menstrual flow was noticed in 4 out of 63 female patients. Menorrhaghia has been described as a bleeding complication in DF in published literature.[22]

Clinically evident pallor was noted in 37 (25%) patients in the present study which was confirmed by low haemoglobin in severe dengue grade compared to other grades, more so in females. This is possibly due to bleeding manifestations or pre-existing nutritional anaemia in the background. Leucopenia was present in 34% of our study population. Some authors reported leucopenia in 62% of patients with severe dengue possibly due to higher total leucocyte count cut-off values of 5000/cmm for defining thrombocytopenia.[23] Leucocytosis was found in 14% of our patients, mostly with severe dengue. Leucocytosis in dengue infection can indicate secondary bacterial infections.[24] Leucocytosis in six out of nine of their patients who had concurrent bacteraemia in a study.[24]

Hepatic dysfunction is a well recognized feature of DF and occurs due to direct involvement of liver cells by dengue virus and by the unregulated host immune response against the virus. It is characterized by hepatomegaly and mild to moderate transaminasitis although jaundice and acute liver failure are uncommon.[20,25] In our study, hepatitis was found in 80.9%, patients including severe hepatitis in 13% of patients. These findings were consistent with reports from another study.[26] We observed that AST elevation was greater than that of ALT in patients with mild-to-moderate hepatitis, whereas, ALT elevation was higher than that of AST in patients with severe hepatitis. Severe hypoalbuminemia was found in 62 (41.9 %) of our patients and this was more evident in patients with severe DF. Liver function abnormalities have been found to be a predictor of mortality in DF in several studies.[27-30] Our observations suggest that AST, ALT serum albumin levels need close monitoring in patients with DF. Presence of

jaundice in patients with DF has been associated with liver failure and by itself is a poor prognostic factor.[30] Jaundice as a symptoms was noted in 7 of our patients while elevated bilirubin was found in 17 (11.5%) of our patients. Similar findings were reported in other studies.[16,31]

Most studies on the mechanisms of bleeding in DHF identified consumptive coagulopathy in a large proportion of cases.[32-35] Coagulopathy is evident in patients with severe DF and shock and is manifested by a prolonged activated partial thromboplastin (aPTT) time.[32] Elevated aPPT was seen in 41% of the study patients. Albuminuria was found in 39 (26.4%) of our patients. Similar findings were reported in another study.[33] Microscopic haematuria was found in 49 (33.1%) of our patients, while a figure of 12.5% was reported in another study.[34] Renal injury comprising increase in serum creatinine, proteinuria, glomerulonephritis, acute kidney injury and haemolytic uremic syndrome have been reported in patients with DF.[35] In our study all patients with renal failure (n=9) had severe DF.

Chest radiographic abnormalities were seen in 37 (25%) of our patients. This included pleural effusion (n=31, 21%) (Figure 3), bilateral infiltrates suggestive of ARDS (n=6, 4%). These abnormalities were found in patients with DF with warning signs and severe DF. In another study,[36] a found higher proportion (53%) of radiographic abnormalities were reported.[36] In another study[37] from China (n=606), ARDS was reported in 1.8% patients.

Ultrasonographic examination of abdomen and chest is useful for the early recognition of severe forms of DF. In our study 29 (19.5%) of the patients had evidence of ascites. Gall bladder wall thickness of more than 5 mm can be adopted as a criterion for identifying dengue patients at high risk for developing hypovolemic shock with a specificity of 92%.[38]Acalculous cholecystitis was found in 12% of our study patients, mostly in patients with severe DF. In a study[39] on pediatric patients with dengue infection, higher proportion had gall bladder wall oedema.

ECG changes in DF include sinus bradycardia, PR prolongation, ST segment elevation and non-specific ST-T changes.[40-42] Myocarditis in DF can manifest with complete AV block or ventricular arrhythmias, which manifest as syncope or palpitations. Most of these changes are transient and usually revert to normal.[40-42]

During the the early part of infection i.e., during the febrile period, dengue virus can be diagnosed by virus isolation in specialized centers. Currently dengue infection can be diagnosed in the first one week of illness with the detection of NS1 antigen. Rapid dengue antigen detection tests can be used in field settings to detect infection in less than an hour.[1] During the primary infection with dengue virus, IgM antibody is the first immunoglobulin isotype to appear and will rise to detectable levels at around 7 days followed by Ig G antibody rise. In contrast during secondary dengue infection, Ig G antibody titers rise rapidly during the first week with lower titers of Ig M though detectable levels. In our study NS1 antigen was detected in 80 (54%) patients who presented to us with fever of less than one week. Rest of the patients who presented late were diagnosed by IgM antibody positivity.

Dengue virus is generally considered non-neurotropic, however, 5 fatal cases of dengue encephalopathy were reported in which dengue virus antigen was detected in the brain by immunohistochemistry.[43]There have been reports of neurological complications of dengue virus infection and include encephalitis, myelitis, GBS and myositis.[44-46] In our study neurological complications were seen in nine patients which included ADEM, GBS and myelitis.

Even though fluid management is the mainstay of treatment, there is no specific therapy for dengue fever. In a recent study[47] from India, *Carica papaya* leaf extract (CPLE) was found to increase the platelet count significantly in DF patients with thrombocytopenia. Further research is required in this area.

The WHO revised the terminology of dengue in year 2012[48] and included unusual manifestations in the form of severe organ involvement such as liver, kidneys, brain or heart. These unusual manifestations may be associated with co-infections, co-morbidities, or complications of prolonged shock.[48] Physicians must be aware of this entity and manage patients more closely.

Oral candidiasis was found in 23 (15.5%) of our patients. In a study[49] from Sri Lanka, oral candidiasis was reported in 18.3% of children with DF. The authors[49] described oral candidiasis as a new finding and proposed increased viral virulence as a cause for oral candidiasis. Transient immunosuppression and antibiotic use could be possible causes for oral candidiasis in patients with DF and this needs further research.

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