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RESEARCH ARTICLE

A retrospective analysis on various clinical outcomes of dengue fever in a tertiary care hospital

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Abstract

Dengue is a vector-borne illness caused by dengue virus-infected female *Aedes* mosquitoes. The main viral strains are DEN1, DEN2, DEN3 and DEN4. Various clinical manifestations are seen as the disease progresses. This observational study was conducted at tertiary care hospitals in and around Mangalore from 2015 to 2019, and included confirmed cases of dengue using immunological studies. Various clinical, laboratory and radiological parameters were recorded and assessed statistically. Dengue was more common in young males (58.9%). Common presentations were fever with headache (94%), hypotension and abdominal pain (15%). Thrombocytopenia (88.4%) and leucopenia (48.3%) were the most common cytological findings. Deranged liver function tests (39.1%) with hyponatremia (35.3%) and low bicarbonate (78.3%) were also seen. Cavitary effusion was seen in 67% of patients with complications. Myocarditis was seen in 2%. Dengue is an easily preventable vector-borne disease, however, its complications can be fatal. Especially in endemic areas, early diagnosis of the disease using clinical, laboratory and radiological assessment is necessary to avoid confusing dengue with other infections due to common symptoms, and for preventing complications.

Keywords

Dengue, Endemic, Thrombocytopenia, Effusion, Radiology

Introduction

Dengue is an acute viral infection caused by the dengue virus, belonging to the family *Flaviviridae*, and is spread by the bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito. Due to its associated symptoms of myalgia and arthralgia, dengue is also termed "breakbone fever" [1]. Dengue fever and its complications have risen continuously over the past 40 years [2]. Annually, 20,000 deaths are recorded globally due to dengue, despite 99% of deaths being avoidable [3]. The clinical spectrum of the disease varies from asymptomatic to severe and fatal forms. Dengue has an incubation period of 4-7 days and may present with an acute high-grade fever, blurred vision, subconjunctival hemorrhage along with retro-orbital pain and arthralgia. Thrombocytopenia occurs in about 70% of dengue patients [3]. In severe cases, it may lead to bleeding under the skin and mucosal surfaces, gastrointestinal bleeding, severe liver pathology, encephalitis, and renal dysfunction [4]. If not managed appropriately, this might also lead to dengue shock syndrome (DSS) [5,6]. Currently, fluid therapy remains the mainstay of treatment for severe dengue [7,8]. In a cohort study conducted in Nicaragua by Gordon et al., secondary infections occur in 59.6 to 115.2 infections per 1,000 persons annually, with the highest incidence in children aged below 5 years [9]. The present research mainly focusses on clinical presentations and the complications associated with dengue fever.

Methods

Study setting

The present observational study was conducted at three tertiary care hospitals in and around Mangalore. Prior permission was obtained from the Medical Superintendent and District Medical Officer.

The study was conducted in accordance with the ethical principles following approval from the Scientific Review and Ethical Committee (IEC KMC MLR 04-16/85). All reported dengue cases in the hospitals were

admitted from 2015 to 2019. All the cases were confirmed with the following laboratory investigations: immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA), nonstructural protein 1 (NS1) Antigen ELISA, and reverse transcription polymerase chain reaction (RT-PCR) [10]. Patients with other viral or bacterial infections after a routine lab test and those who refused to participate in the survey were excluded from the study.

Statistical analysis

Data obtained was recorded in Microsoft Excel and analysis was done using SPSS version 16.0. Results were presented using tables and figures.

Results

The total patients of 1,474 were enrolled. Among them, 869 (58.9%) were males and 606 (41.4%) were females. Among them, 942 (63.9%) were married and 532 (36.1%) were unmarried. Most of the patients were manual laborers. The age range was 1 year to 85 years. There were 351 patients belonging to the 20-30 years age group, of which 231 were males and 120 were females (Figure 1). Most patients were from Mangalore. The 731 patients from outside of Mangalore were from Belathangady, Sullia, Puttur, Bantwal, Udupi, Bangalore, Moodbidri, Davangere, Karwar, Coorg, Belgaum, Uttara kannada, Shimoga, Chikkamagalur, Hassan, Haveri, Bagalkote, Gadag, Koppal, and Chitra Durga. Nine patients were from other states, including West Bengal, Madhya Pradesh, Pune, Uttar Pradesh, Rajasthan, Assam, Mumbai, and Andhra Pradesh. Fever with headache was the most common symptom, while hypotension along with abdominal pain were the most frequent signs (Table 1). Forty-eight cases were admitted to the intensive care unit due to hematological complications. Twelve patients had macrophage activation syndrome. Pancytopenia was seen in five patients. Disseminated intravascular coagulation (DIC) and deep venous thrombosis (DVT) were complications in one of the patients (Table 2). Laboratory investigations were categorized into high, normal and low levels. Electrolytic imbalances were observed, particularly hyponatremia (35.3%) and low bicarbonate levels (78.8%) (Table 3), however, there were no significant statistical correlations between either hyponatremia ($\chi^2\{1,N=1474\}=2.0047$, $p=0.156815$; $p>0.05$) nor low bicarbonate levels ($\chi^2\{1,N=1474\}=1.4764$, $p=0.224338$; $p>0.05$), with respect to the complications of dengue fever. Chest X-ray was done in 324 patients, out of which 9.25% had pleural effusion. Pneumothorax was seen in three patients. Ultrasonography (USG) (Table 4) revealed changes in liver parenchyma of 106 patients and hepatomegaly in 89 out of 358 patients who underwent the scan. Overall, 132 scans showed gallbladder wall edema while 127 patients had ascites and 82 patients had splenomegaly. Gallstones were found in 19 patients and portal hypertension in nine patients. Among the 19 patients subjected to brain scans, cerebral edema was observed in three patients, and ischemic changes were seen in two patients. Post-viral demyelination was observed in one patient. Electrocardiography (ECG) and echocardiography (Table 4) revealed sinus tachycardia in 21 patients, ST elevation in 13 and T-wave abnormalities. These changes are suggestive of myocarditis. Myocardial infarction was seen in ten patients. Pericarditis and pericardial effusion were each seen in one patient. Left ventricular hypertrophy was seen in 27 patients.

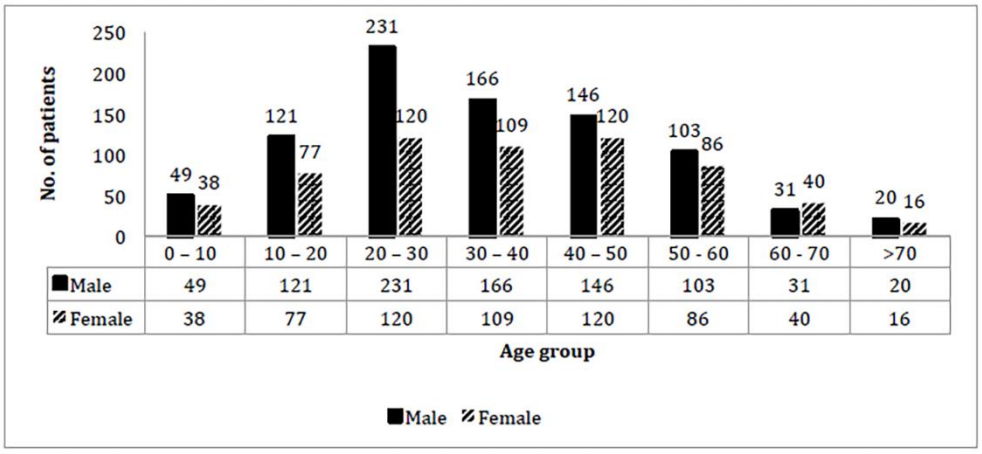

Figure 1. Cross-tabulation of Dengue Fever with Age Group and Gender

Table 1. Symptoms and Signs of Patients with Dengue Fever

Symptoms (Seen in >10 % of sample size)	**N**	**%**
High grade fever	1385	94
Headache	604	41
Vomiting	467	31.7
Myalgia	332	22.5
Generalized body ache	289	19.6
Generalized weakness	229	15.5
Dizziness	185	12.6
Pain in the abdomen - Generalized	176	11.9
Symptoms (Seen in 1 – 10 % of sample size)		
Nausea	135	9.2
Loose stools	127	8.6
Arthralgia	103	7
Decreased appetite	95	6.4
Low grade fever	85	5.8
Dry cough	83	5.6
Cough with expectoration	80	5.4
Backache	78	5.3
Melena	45	3.1
Retro-orbital pain	39	2.6
Breathlessness	33	2.2
Vaginal bleeding	33	2.2
Rash	32	2.2
Epigastric pain	31	1.7
Common cold	25	1.5
Gum bleeding	22	1.2
Decreased urination	17	1.2
Increased menstrual bleed	17	1.2
Burning micturition	17	1.2
Disorientation	16	1.1
Symptoms (<1 %)		
Constipation	15	1
Hematuria	14	1
Paralysis	9	0.6
Loss of vision	8	0.5
Hiccups	7	0.5
Epistaxis	7	0.5
Throat pain	6	0.4
Pedal edema	6	0.4
Altered sensorium	6	0.4
Jaundice	4	0.3
Generalized tonic-clonic seizure	3	0.2
Weight loss	3	0.2
Abdominal distension	3	0.2
Hematemesis	2	0.1
Chest pain	2	0.1
Watering of eyes	2	0.1
Itching	2	0.1
Hemoptysis	1	0.1
Signs	**N**	**%**
Hypotension	110	7.5
Abdominal tenderness	110	7.5
Splenomegaly	58	3.9
Hepatomegaly	56	3.8

Petechiae	48	3.3
Postural drop	41	2.8
Lymphadenopathy	40	2.7
Pitting edema	31	2.1
Tachypnoea	23	1.6
Pallor	20	1.4
Tourniquet test	19	1.3
Rhonchi - Bilateral	18	1.2
Blanching erythematous maculopapular rash	22	1.5
Diffuse crepitations	15	1
Conjunctival congestion	14	1
Periorbital puffiness	14	1
Skin flushing	13	0.9
Decreased breath sounds	11	0.7
Deep tendon reflex decreased	10	0.7
Tongue coating	9	0.6
Signs (≤ 0.5%)		
Dehydration	7	0.5
Glossitis	7	0.5
Disorientation	7	0.5
Shifting dullness	6	0.4
Conjunctival hemorrhage	6	0.4
Facial rash	5	0.3
Bradycardia	5	0.3
Macular edema	5	0.3
Tachycardia	5	0.3
Dry tongue	4	0.3
Icterus	4	0.3
Meningitis signs	4	0.3
Anasarca	4	0.3
Throat congestion	3	0.3
Ecchymosis	3	0.3
Romberg's sign positive	3	0.2
Neck stiffness	3	0.2
Nystagmus	2	0.1
Sinus tenderness	1	0.1
Systolic murmur	1	0.1
Clubbing	1	0.1
Bell's palsy	1	0.1

Table 2. Complications of the Dengue Fever Patients

Complications	***N (170)***
Needing Intensive Care Unit admission (unstable hemodynamics)	48
Dengue shock syndrome	10
Thrombophlebitis	10
Macrophage activation syndrome	9
Acute kidney injury	8
Lower respiratory tract infection	6
Sepsis	5
Acute respiratory distress syndrome	5
Pancytopenia	5
Encephalitis	5
Hepatitis	4
Uro-sepsis	4
Myocarditis	4
Pancreatitis	4
Dengue hemorrhagic fever	3
Malaria	3
Secondary hemophagocytic lymphohistiocytosis	3
Exacerbation of Asthma	2
Leptospirosis	2
Hematoma - site of needle prick	2
Acute hemorrhagic leukoencephalitis	2
Serositis	2
Multi-organ dysfunction	2
Meningitis	2
Perianal abscess	2
Complications (≤ 1 %)	
Corona radiata infarct	1
Suspected rheumatic regurgitation	1
Severe hepatic encephalopathy	1
Vesicoureteric junction calculus	1
Guillain-Barré syndrome	1
Poststreptococcal glomerulonephritis	1
Cytomegaloviral retinitis	1
Tonsilitis	1
Disseminated intravascular coagulation	1
Polycystic ovarian disease	1
Enteric fever	1
Deep venous thrombosis	1
Angle closure glaucoma	1
Bell's palsy	1
Spastic diplegia	1
Hypokalemic periodic paralysis	1
Sensorineural hearing loss	1
Uterine myoma	1

Table 3. Laboratory Profile of the Dengue Fever Patients

Laboratory investigations	High, N (%)	Normal, N (%)	Low, N (%)
Hemoglobin	345 (24.8)	1026 (73.7)	21 (1.5)
White Blood Cells	87 (6.3)	630 (45.4)	670 (48.3)
Platelets	13 (0.9)	157 (10.7)	1295 (88.4)
Neutrophils	138 (10.8)	913 (71.3)	230 (18)
Lymphocytes	310 (24.2)	581 (45.4)	390 (30.4)
Monocytes	457 (38.1)	598 (49.8)	145 (12.1)
Eosinophils	42 (5)	341 (40.6)	456 (54.4)
Basophils	67 (14.6)	391 (85.4)	0 (0)
RBC count	13 (5.5)	182 (76.8)	42 (17.7)
Mean Corpuscular Volume	9 (3.4)	221 (83.7)	34 (12.9)
Mean Corpuscular Hemoglobin	17 (6.6)	160 (61.8)	82 (31.7)
Mean Corpuscular Hemoglobin Concentration	5 (1.9)	42 (16)	215 (82.1)
Red cell Distribution Width	72 (29.3)	171 (69.5)	3 (1.2)
Reticulocyte	4 (40)	1 (10)	5 (50)
Creatinine	53 (4)	1116 (85.2)	141 (10.8)
Urea	63 (6.5)	807 (83.3)	99 (10.2)
Sodium	4 (0.4)	642 (64.3)	352 (35.3)
Potassium	17 (1.7)	811 (81.3)	170 (17)
Chloride	11 (2.1)	342 (66)	165 (31.9)
Bicarbonate	17 (3.3)	91 (17.8)	402 (78.8)
AST	902 (74.2)	311 (25.6)	2 (0.2)
ALT	677 (52.8)	589 (45.9)	16 (1.2)
ALP	180 (25.2)	589 (45.9)	16 (1.2)
Total Bilirubin	81 (7.5)	963 (89.5)	32 (3)
Direct Bilirubin	185 (20)	542 (58.5)	200 (21.5)
Total Protein	2 (0.3)	406 (60.6)	262 (39.1)
Albumin	1 (0.1)	563 (77.7)	161 (22.2)
Globulin	72 (10.9)	436 (66.1)	152 (23)
Calcium	0 (0)	53 (41.7)	74 (58.3)
Phosphate	7 (9.2)	31 (40.1)	38 (50)
Magnesium	1 (3.3)	21 (70)	8 (26.7)
Uric Acid	2 (3.4)	37 (63.8)	19 (32.8)

Table 4. Radiological, ECG and Endoscopic findings in Dengue Patients

Chest X-ray	**No of cases (N=324)**
Normal	272
Pleural effusion	30
Mild pleural effusion	7
Lower respiratory tract infection / Acute respiratory distress syndrome	7
Pulmonary congestion	5
Bilateral opacity	5
Lung collapse	3
Consolidation	2
Chronic obstructive pulmonary disease	1
USG abdomen	**(N=358)**
Normal	76
Gall bladder wall edematous	132
Minimal ascites	122
Hepatomegaly	89
Fatty liver	85
Mild pleural effusion	68
Splenomegaly	56
Pleural effusion	46
Grade 1 renal parenchymal changes	35
Mild splenomegaly	26
Altered liver echotexture	21
Cholelithiasis	19
Renal calculus - urolithiasis	16
Portal hypertension	9
Prostatomegaly	8
Hydroureteronephrosis	7
Moderate ascites	5
Gall bladder sludge	2
Retroperitoneal collection	2
Pyelonephritis	2
Perinephric fluid collection	2
Urinary bladder thickening	1
Splenic cyst	1
Splenic infarct	1
Intrauterine growth restriction	1
Mesenteric lymphadenitis	1
Magnetic Resonance Imaging - Head	**(N=6)**
Normal	2
Corona radiata infarct	1
Intraventricular bleed	1
Post-viral demyelination	1
Cerebral edema	1
Computerized Tomography scan - Abdomen	**(N=4)**
Normal	1
Retroperitoneal hemorrhage	2
Inferior epigastric artery rupture	1
Computerized Tomography scan - Head	**(N=13)**
Normal	9
Cerebral edema	2
Encephalitis	1
Ischemic changes	1
Electrocardiography	**(N=150)**
Normal	65

Left ventricular hypertrophy	22
Sinus tachycardia	21
Sinus bradycardia	16
ST elevation	13
Myocardial infarction	10
Inverted T wave	10
Atrioventricular block	6
Poor R wave progression	4
QT prolongation	3
Ventricular ectopia	2
Left atrial enlargement	2
Atrial fibrillation	1
Echocardiography	**(N=29)**
Normal	20
Left ventricular hypertrophy	5
Pericardial effusion	1
Pericarditis	1
Atrial septal defect	1
Aortic regurgitation	1
Endoscopy	**(N=5)**
Normal	4
Mallory Weiss tears	1

Discussion

The current study, after approval from the Scientific Review and Ethical Committee, and Hospital administration, was conducted to illustrate the different clinical, epidemiological and laboratory parameters of dengue patients attending our hospitals. It aims to explore the clinical profile of dengue so to help in management of dengue patients, especially those with complications. The study was conducted on 1,474 patients who were confirmed positive for dengue fever. It was found that most cases occurred in younger adults aged between 20 and 30 years of age. The results of this study show that, in the second decade of life, dengue fever is more common in males when compared to females.

A prospective study conducted in Mangalore found that 40.6% of patients presented with hepatitis as the most common atypical manifestation [11]. A study conducted by Padhi et al. in southern Odisha, India, in 2012, found that 97.58% of patients presented with dengue fever, 2.24% with dengue hemorrhagic fever (DHF) and 0.18% presented with DSS. They also found that a majority (47.86%) of the patients presented during the month of September [12].

The present research is in accordance with other studies [13,14,15,16,17] which also show male predominance with infection. However, the exact mechanism behind this is still unknown. Most of the infections were seen in suburban areas of coastal cities. In dengue fever patients, arthralgia, myalgia, retro-orbital pain, rash, and hemorrhagic signs normally appear with a series of symptoms. In the present research, dengue fever was associated with pulmonary symptoms, gastrointestinal disorders, bradycardia, thrombocytopenia, and deranged liver function tests. Previous studies [14,16,17,18,19] (especially after outbreaks in 2010 and 2018) also document the wide range of clinical signs and symptoms associated with dengue fever, which is in accordance with our study. Most of the complications were hematological or vascular in nature, occurring in about 25% of the total number of complications, of which dengue shock syndrome (6%) and thrombophlebitis (6%) were the most frequent. The reason behind this was thrombocytopenia and perched capillary permeability. Most of our patients suffering from Acute Respiratory Distress Syndrome (ARDS) and post-dengue hematological and vascular complications required ICU admissions. It was also noted that, although dengue disease is easily prevented, prognosis worsens rapidly once complications occur (particularly if they are hemorrhagic or neurological in nature, or cavitary effusions). The total case fatality rate was 1.08% and all had succumbed following complications of dengue. It was observed that among the patients who suffered from complications, 9.4% died (Table 5). Sepsis was the major cause of mortality (56.2%) among patients suffering from complications of dengue. The neutropenia observed in our study was in agreement with the findings of Singh et al., who also noticed leucopenia [15]. This might have been a possible sequelae of myeloid progenitor cells being damaged by the virus. It was found that the risk of severity depended mostly on hematocrit, thrombocytopenia, leukopenia and LFT, similar to previous studies [13,16,17,19,20,21,22]. Serum ferritin was also found to be elevated in severe cases requiring ICU admissions in our study. This was noted to be more effective in assessing younger patients [21]. A study by Ab-Rahman et. al [23] showed that sCD163 is a good predictive marker, similar to ferritin, for assessing severity. Ascites and pleural effusion were the most frequent cavitary

complications in our study. A similar incidence of ascites and pleural effusion has also been observed in dengue patients in other studies [16,17,19,20]. Myocarditis, though rare, was the most common cardiological complication and was also reported by previous studies [1]. This emphasizes the need to heed ECG changes in patients hospitalized for dengue. Our study also shows that co-infections, like leptospirosis and malaria, must be excluded before the disease progresses further. It was noted previously [1] that chikungunya often occurs concurrently with dengue. However, there is no concrete evidence to show a positive correlation between the co-existence of these infections. In recent years, the prevalence of dengue fever has increased, as an endemic infection seen increasingly in the developed parts of the world. The current study assesses the clinical features of dengue fever along with other syndromes. The study is also supported by radiological investigations. There was a statistically significant association between the use of early radiological investigation and detection and management of cavitary complications of dengue fever ($\chi^2\{1,N=1474\}=8.301$, $p=0.0039612$; $p<0.05$). The radiological profile showed signs such as thickened gallbladder wall, free fluid in the abdomen and hepatomegaly. This could be associated with the increased incidence (11.9%) of dengue fever patients complaining of abdominal pain. The findings of edematous and thickened gall bladder, atypical acalculous cholecystitis and hepatosplenomegaly were in concordance with the other studies [16,18]. This case series confirms the incidence of multiple central nervous system (CNS) manifestations, similar to previous reports [1,3,18,19] of dengue virus infection, and sheds light on the necessity of considering dengue as a key differential diagnosis of acute encephalitis syndrome. Furthermore, these findings imply a strong indication for radiological evaluation of patients infected with dengue as a routine clinical investigation. The strength of this study is that it has comprehensively collected the clinico-epidemiological, laboratory and radiological findings of dengue complications in an endemic area.

Table 5. Cause of Death in Complicated Dengue Patients

Cause of death	N (16)
Sepsis	9
Multi-organ Dysfunction	4
Acute Respiratory Distress	2
Chronic Liver Disease	1

Conclusions

In conclusion, doctors in dengue-endemic areas should look for both typical (primarily thrombocytopenia) and atypical manifestations of dengue (especially neurological deficits), rule out other infections and use prompt investigations, including radiological tests and prognostic markers like serum ferritin, to manage the disease. Close monitoring of platelet count, packed cell volume (PCV) and LFT is important, in particular for patients aged below 5 years. While hyponatremia was not statistically shown to have an association with prognosis of the cases with complications, early radiological investigations (chest X-ray and USG of the abdomen) were found to have a positive association with detecting and managing complications secondary to dengue fever. Strict surveillance and assessment of atypical manifestations are needed to prevent morbidity and mortality associated with dengue.

Conflicts of interest

All authors declared no conflicts of interest.

Declarations - Author contribution statement

Akash Kumar- Contributed to conception, data collection, analysis, writing of original draft, editing and finalising the version to be submitted. Adarsh Sugathan- Contributed to writing the original draft, editing, and finalising the version to be submitted. Nayanatara Arun Kumar- Contributed to the conception of the study, supervised, analysed, wrote the original draft, edited, and finalised the version to be submitted. Basavaprabhu Achappa- Contributed to the supervision of the study, edited and finalised the version to be submitted. All authors have read and approved the final version of the manuscript to be submitted.

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Data accessibility statement

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request to the corresponding author.

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