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Original Research Article

A Study of Clinical Profile of Dengue Fever, with Special Reference to its Complications

Anudeep Reddy K.[1], Niranjan N.[2]

[1]Assistant Professor, Department of General Medicine, Navodaya Medical College, Raichur, Karnataka, India.
[2]Assistant Professor, Department of Pulmonary Medicine, Navodaya Medical College, Raichur, Karnataka, India.

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Corresponding author: Dr. Anudeep Reddy K
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Abstract

Background: In this study, we wanted to evaluate the clinical profile of the dengue cases, assess the clinical manifestations of the disease and their incidence, evaluate the complications related to different organ systems and study the outcome of the dengue virus infection in patients enrolled.

Materials and Methods: This was a hospital-based study conducted among 301 patients who presented with dengue fever to the concerned department at Vijayanagara Institute of Medical Sciences, Bellary, over 18 months after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: Most of the respiratory complications were seen among patients with severe dengue (54.2%) compared to the rest of the clinical types of dengue and dengue with warning signs (42.3%). Clinical types of dengue were found to be statistically significant ($p < 0.001$). Cardiovascular complications were seen among patients with severe dengue (12.2%). Complications among the different clinical types of dengue were found to be statistically significant ($p < 0.012$). Increased renal function test suggestive of acute kidney injury was the common complication in both severe dengue 16 cases (21.6%). The proportion of abdominal complications among the different clinical types of dengue was found to be statistically significant ($p < 0.001$). All CNS complications were seen among patients with severe dengue (32.4%). CNS complications among the different clinical types of dengue were found to be statistically significant ($p < 0.001$). The haematological complications were seen among patients with dengue with warning signs (45.5%) compared to the rest of the clinical types of dengue-like severe dengue (2.8%). Complications among the different clinical types of dengue were found to be statistically significant ($p < 0.001$).

Conclusion: Clinical and experimental observations suggest that liver involvement occurs during dengue infections. Clinical evidence includes hepatomegaly and increased serum liver enzymes, with liver involvement being more pronounced in the more severe forms of infection. Dengue viral antigens have been found within hepatocytes, and the virus appears to replicate in both hepatocytes and Kupffer cells, and dysregulated host immune responses may play an important causative role in liver damage. Modulating these immune responses may have therapeutic potential.

Keywords: Clinical Profile of Dengue Fever, Complications

Introduction

Dengue infection, an arthropod-borne viral hemorrhagic fever, continues to be a major challenge to public health, especially in South-East Asia. [1] It has a wide geographical distribution and can present a diverse clinical spectrum. [2] Although dengue virus is a non-hepatotoxic virus, liver injury due to dengue infection is not uncommon and has been described since the 1960s. [3]

In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of a worse prognosis. [4] The liver dysfunction could be a direct viral effect or an adverse consequence of dysregulated host immune response against the virus. Cardiac complications include reduced ejection fraction, global hyperkinesia, pericardial effusion, abnormal systolic and diastolic dysfunction and arrhythmias. [5,6,7] Respiratory complications due to increased permeability and disruption of alveolar-capillary barrier results in oedema of interstitial spaces deteriorating pulmonary function causing pneumonia, sepsis and ARDS.[8,9] Several neurological complications include Bell's palsy, GBS, delirium, paraparesis, and myositis. There are renal complications along with electrolytes, acid-base disorders, dermatological, and rheumatologic complications. [10,11,12]

Aims and Objectives

- To assess the clinical manifestations of the disease and their incidence
- To evaluate the complications related to different organ systems in patients enrolled in this study.
- To study the outcome of the dengue virus infection in patients enrolled in the study.

Materials and Methods

This was a hospital-based study conducted among 301 patients who presented with dengue fever to the concerned department at Vijayanagara Institute of Medical Sciences, Bellary, over 18 months after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Patients who gave consent to participate in the study.
- Dengue IgM positive or NS1 antigen positive
- Age more than 16 yrs.
- Platelet count less than 1,50,000.

Exclusion Criteria

- Other causes of fever with thrombocytopenia like malaria, brucella, leptospira, enteric fever, drug-induced and viral and rickettsial fever cause other fevers caused by normal platelets and where NS1 antigen and IgM dengue antibody are negative.
- Pre-existing cardiac failure and arrhythmias, respiratory, hepatic, renal, haematological, and neurological disorders.
- Age < 16 yrs.

Statistical Methods

The collected data were entered into an excel data sheet after appropriate data filtration, the data sheet was transferred and analysed using SPSS version 20 software. Appropriate descriptive statistics like percentage/proportions, mean and standard deviation were used to describe the data. Appropriate tests of significance like the chi-square test and student t-test were used to study the association between the study variables and the outcome of the variables. A 'P' value less than 0.05 was considered statistically significant.

Results

Table 1: Demographic Distribution

Age group	Frequency	Percent
≤ 20 yrs.	32	10.6
21 - 30 yrs.	68	22.6
31 - 40 yrs.	66	21.9
41 - 50 yrs.	54	17.9
51 - 60 yrs.	43	14.3
> 60 yrs.	38	12.6
Total	301	100
Mean ± SD	40.48 ± 16.26	
Age Distribution		
Sex	**Frequency**	**Percent**
Female	104	34.6
Male	197	65.4
Total	301	100
Sex Distribution		

A total of 301 patients diagnosed with dengue were included in the study wherein 44.5% were in the age group of 21 – 40 years followed by 41 – 60 years (32.2%), 12.6% were elderly patients and 10.6% of them were less than 20 years. The mean age of the patients was 40.48 years with a standard deviation of 16.26 years.

There was a male preponderance with nearly two-thirds of the patients being males (65.4%) and the remaining 34.6% were females with a female-to-male ratio of 1:1.89.

Clinical profiling of the patients, especially examining the vital signs of the patients revealed that 14.3% were drowsy, 1.3% of them were in a coma and on examining the pulse rate, 2% of them had bradycardia and 41.5% of them had tachycardia. On measuring the blood pressure at the time of admission, it was found that 7% of the patients had hypotension, one patient had hypertension and the remaining 92.7% of them had normal blood pressure.

On cardiovascular examination, tachycardia was found in 41.5% of the patients and bradycardia was seen in 2% of the cases. In two cases, LVS3 was found and the rest of the patients 97.3% were normal.

Table 2: Clinical profile of the patients, vital signs, sensorium and systemic examination findings

Vital signs	Frequency	Percent
Consciousness		
Coma	4	1.3
Drowsy	43	14.3
Normal	254	84.4
Pulse rate		
Bradycardia	6	2
Tachycardia	125	41.5
Normal	170	56.5
Systolic BP		
Hypertension	1	0.3
Hypotension	21	7
Normal	279	92.7

Clinical profile of the patients, vital signs and sensorium		
Systemic findings	**Frequency**	**Percent**
CVS findings		
Bradycardia	6	2
Tachycardia	125	41.5
LV S3	2	0.7
Normal	293	97.3
CNS findings		
Coma b/l extensor	10	3.3
Drowsy	2	0.7
GBS	2	0.7
Hemiplegia	7	2.3
Meningitis/encephalitis	8	2.7
Paraplegia	1	0.3
Normal	271	90
Clinical profile of the patients, systemic examination findings		

On CNS examination, higher motor function examination revealed that 3.3% of the patients were in a coma with bilateral extensor response and two cases were drowsy. Signs suggestive of meningitis/encephalitis were observed in 2.7% of the cases, hemiplegia in 2.3% and one patient with paraplegia were observed. Two cases had Guillain Barre Syndrome and the rest 90% of the patients were normal.

Renal function tests revealed that serum creatinine levels of more than 1.2 mg/l suggestive of acute kidney injury were observed in 18.6% of the patients and the rest of the patients (81.4%) had normal serum creatinine levels. On urine examinations, haematuria was observed in 3.7%, and albuminuria was seen in 0.7% of the cases.

Table 3: RFT parameters, Renal function parameters and Haematological findings among the patients

RFT parameters	Frequency	Percent
Serum Creatinine levels		
Acute kidney injury	56	18.6
Normal	245	81.4
Total	301	100
Urine findings		
PRO 3+	2	0.7
RBC 3+	**11**	3.7
Normal	288	95.7
Total	301	100
Renal function parameters among the patients		
Parameters	Frequency	Percent
Haemoglobin levels		
Anaemia	131	43.5
Normal	170	56.5
Total leucocyte count		
Leucocytosis	46	15.3
Leucopenia	25	8.3

Normal	230	76.4
Platelet response to treatment		
No response	7	2.3
Responsive	294	97.7
Haematological findings among the patients		

The haematological profile of the patients revealed that 43.5% of them were anaemic, leucopenia was noted in 8.3% and leucocytosis was seen in 15.3%. The majority of the patients responded to the treatment as evidenced by improved platelet count whereas in 2.3% of the cases the platelet count did not improve to the treatment and all these patients eventually died.

Most of the respiratory complications were seen among patients with severe dengue (54.2%) compared to the rest of the clinical types of dengue, dengue with warning signs (42.3%). There were no complications among patients with only dengue fever. This difference in the proportion of complications among the different clinical types of dengue was found to be statistically significant ($p < 0.001$). ARDS (51.4%) was the commonest complication in severe dengue and pleural effusion (42.3%) was common among patients with dengue with warning signs.

Table 4: Comparison of respiratory, CVS and abdominal complications among different types of clinical dengue

Respiratory complications	**Clinical types of dengue**			
	Dengue fever	Dengue with warning signs	Severe Dengue	P value
ARDS	0 (0.0)	0 (0.0)	38 (51.4)	0.000
Pleural effusion	0 (0.0)	39 (42.3)	1 (1.4)	
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (1.4)	
No complication	135 (100.0)	53 (57.7)	34 (45.9)	
Total	135 (100.0)	92 (100.0)	74 (100.0)	
Comparison of respiratory complications among different types of clinical dengue				
CVS complications	**Clinical types of dengue**			
	Dengue fever	Dengue with warning signs	Severe Dengue	P value
1 DEG AV BLOCK	0 (0.0)	0 (0.0)	1 (1.4)	0.012
2 DEG AV BLOCK	0 (0.0)	0 (0.0)	3 (4.1)	
AWMI	0 (0.0)	0 (0.0)	1 (1.4)	
CCF	0 (0.0)	0 (0.0)	1 (1.4)	
S. HYPO	0 (0.0)	0 (0.0)	1 (1.4)	
SVT AVNRT	0 (0.0)	0 (0.0)	1 (1.4)	
VT	0 (0.0)	0 (0.0)	1 (1.4)	
Pericardial effusion	0 (0.0)	20 (21.7)	0 (0.0)	
No complication	135 (100.0)	72 (78.3)	65 (87.8)	
Total	135 (100.0)	92 (100.0)	74 (100.0)	
Comparison of CVS complications among different types of clinical dengue				
Abdominal complications	**Clinical type of dengue**			
	Dengue	Dengue with warning	Severe	P

	fever	signs	Dengue	value
Acute appendicitis	0 (0.0)	2 (2.2)	0 (0.0)	0.000
Acute glomerulonephritis	0 (0.0)	1 (1.1)	0 (0.0)	
Acute pancreatitis	0 (0.0)	4 (4.3)	1 (1.4)	
Acute hepatitis	0 (0.0)	0 (0.0)	1 (1.4)	
Ascites	0 (0.0)	2 (2.2)	0 (0.0)	
Increase RFT	0 (0.0)	11 (12.0)	16 (21.6)	
Glomerulonephritis	0 (0.0)	1 (1.1)	0 (0.0)	
Inguinal abscess	0 (0.0)	1 (1.1)	0 (0.0)	
No complication	135 (100.0)	71 (77.2)	56 (75.7)	
Total	135 (100.0)	92 (100.0)	74 (100.0)	
Comparison of abdominal complications among different types of clinical dengue				

All cardiovascular complications were seen among patients with severe dengue (12.2%). Among them, 2nd degree AV block 3 cases (4.1%) was the commonest complication in severe dengue and one case each of 1st degree AV block, AWMI, congestive cardiac failure, systemic hypotension, SVT AVNRT and ventricular tachycardia was noted. There were no complications among patients with only dengue fever and dengue with warning signs. This difference in the proportion of CVS complications among the different clinical types of dengue was found to be statistically significant ($p < 0.012$).

Table 5: Comparison of liver enzymes among different clinical types of dengue

Parameters		Clinical types of dengue			
		Dengue fever	Dengue with warning signs	Severe Dengue	P value
AST	> 1000 IU	0 (0.0)	0 (0.0)	7 (9.5)	0.000
	101 - 200 IU	61 (45.2)	38 (41.3)	23 (31.1)	
	200 - 1000 IU	0 (0.0)	43 (46.7)	32 (43.2)	
	40 - 100 IU	0 (0.0)	1 (1.1)	2 (2.7)	
	Normal	74 (54.8)	10 (10.9)	10 (13.5)	
	Total	135 (100.)	92 (100.0)	74 (100.0)	
ALT	> 1000 IU	0 (0.0)	0 (0.0)	3 (4.1)	0.000
	101 - 200 IU	61 (45.2)	29 (31.5)	27 (36.5)	
	200 - 1000 IU	0 (0.0)	49 (53.3)	36 (48.6)	
	40 - 100 IU	1 (0.7)	8 (8.7)	3 (4.1)	
	Normal	73 (54.1)	6 (6.5)	5 (6.8)	
	Total	135 (100.)	92 (100.0)	74 (100.0)	
ALP	> 500 IU	0 (0.0)	2 (2.2)	2 (2.7)	0.000
	101 - 200 IU	27 (20.0)	29 (31.5)	28 (37.8)	
	201 - 500 IU	32 (23.7)	39 (42.4)	24 (32.4)	
	44 - 100 IU	0 (0.0)	14 (15.2)	7 (9.5)	
	Normal	76 (56.3)	8 (8.7)	13 (17.6)	
	Total	135 (100.)	92 (100.0)	74 (100.0)	

Increased renal function test suggestive of acute kidney injury was the common complication in both severe dengue in 16 cases (21.6%) and dengue with warning signs in 11 cases (12%), however the proportion of acute kidney injury was

more (21.6%) in severe dengue compared to dengue with warning signs (12%). Complications such as acute pancreatitis, acute appendicitis, acute glomerulonephritis, ascites and inguinal abscess were more in patients suffering from dengue with warning signs compared to severe dengue. This difference in the proportion of abdominal complications among the different clinical types of dengue was found to be statistically significant ($p < 0.001$).

Comparing the liver function test parameters especially liver enzymes among the different clinical types of dengue revealed that the proportion of raised serum levels of AST was high in dengue with warning signs (89.1%) and severe dengue (86.5%) compared to only dengue fever cases (45.2%) and this difference in the proportion of AST levels among the different clinical groups was found to be statistically significant ($p < 0.001$). AST levels of more than 1000 IU were seen only in severe dengue (9.5%) which was not observed in other clinical types.

Similarly, the proportion of raised serum levels of ALT was high in dengue with warning signs (93.5%) and severe dengue (93.2%) compared to only dengue fever cases (45.9%) and this difference in the proportion of ALT levels among the different clinical groups was found to be statistically significant ($p < 0.001$). ALT levels of more than 1000 IU were seen only in severe dengue (4.1%) which was not observed in other clinical types.

Following the same pattern of AST and ALT, the proportion of raised serum levels of ALP was high in dengue with warning signs (91.3%) and severe dengue (82.4%) compared to only dengue fever cases (43.7%) and this difference in the proportion of ALP levels among the different clinical groups was found to be statistically significant ($p < 0.001$).

Discussion

In our study, we have classified it as dengue fever, dengue fever with warning signs and severe dengue here; we wanted to analyze the present study by comparing it with other dengue adult studies. Indian and other South Asian region studies are taken up for discussion.

Dengue Fever (DF) occurred in 135(45%) patients. Dengue with warning signs occurred in 92 (30%) and severe dengue in 74 (24.6) patients. Our study is comparable with Malavage et al, Janak et al in which DF was 30.6 % and 46% respectively, and DHF was 69 % and 54% respectively. In our study on general physical examination and vitals, icterus more severe in dengue, which is supported by the study of Rajoo et al. Hypotension had also been correlated with the severity of dengue.

In our study, hyperbilirubinemia was significantly more common in patients with dengue with warning signs and severe dengue when compared to DF patients. Rajoo et al. [13] found hyperbilirubinemia to be significantly more common in patients with DSS, DF patients with haemorrhage and non-survivors. Biochemical liver dysfunction, in the form of increased transaminases, was found in most of the patients in our study 96.6% - 99.3%, similar to the results of Rajoo et al. [13] (93.9%–97.7%) and other studies. However, in a study by Souza et al. [14] AST and ALT were deranged only in 63.4% and 45% of patients respectively. In our study, increased levels of ALP and serum bilirubin were noted in a smaller proportion of patients, as with the results of Rajoo et al. [13] and Itha et al. [15]

Most of the cases with ARDS presentation belonged to severe dengue. In our study, the most common symptoms in the ARDS group were fever, melena and abdominal pain and the most common signs were facial puffiness and hepatomegaly.

90% of the ARDS patients had a platelet count of less than 50,000 indicating that

low platelet counts predispose to the development of ARDS in the presence of associated haemorrhagic manifestations. However, in the other groups without respiratory manifestations, 73% had a platelet count in the range 50,000-150000.

In our study, out of 300 cases of dengue that were studied, 28 showed cardiac involvement. Therefore, the incidence of cardiac involvement in our study was 2.3%. In a study conducted by Ranjit S.108 in Chennai in 2001-03, out of 858 cases of dengue fever studied, the incidence of cardiac involvement was 4.5%.

In a study conducted by Niranjan et al, it was observed that 26 patients with dengue infection who were admitted to our institution in the last 2 years presented with various neurological complications. The age of the patients ranged from 11 to 60 years (mean age, 29.08 years). Eighteen patients were males. The demographic and clinical profile of these patients is described in. In our study, we found varied neurological manifestations involving almost all parts of the nervous system. We categorized our observations into three groups based on the possible pathogenic mechanism: (1) neurotropic complications - encephalitis, myelitis, myositis, and (2) Systemic complications - hypokalemic paralysis and (3) post-infectious immune-mediated.

In our study, we noticed renal involvement in 27 cases causing AKI IN 27 cases, inguinal abscess in one patient, and glomerulonephritis in one patient. It was in around 10% of cases there was AKI in 0%, 30 %, and 70 % of DF, DF with warning signs and severe dengue. Our study is on par with studies of Joa Fernando et al [16] and others.

In our study, we noted pancreatitis in 5 patients of 300 patients with increased amylase and lipase levels, about 4 times the upper normal limits. Our study is not on par with the study by Gangaramusham et al who noticed pancreatitis in 15 patients of 300 dengue patients. [17]

In the comparison of the fatality rate in our study, it was observed that 7 dengue deaths were severe dengue cases out of 301 cases studied over 18 months about 2.33% of the mortality rate. It was found that the age distribution was extreme of ages about 30% of death between 15 and 20 yrs. and 65% of death above 65 yrs., indicating a bimodal peak in mortality.

Conclusion

Clinical and experimental observations suggest that liver involvement occurs during dengue infections. Clinical evidence includes hepatomegaly and increased serum liver enzymes, with liver involvement being more pronounced in the more severe forms of infection. Dengue viral antigens have been found within hepatocytes, and the virus appears to be able to replicate in both hepatocytes and Kupffer cells, and dysregulated host immune responses may play an important causative role in liver damage. Modulating these immune responses may have therapeutic potential.

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