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Changing Trends in Clinical Presentation and Biochemical Spectrum of Dengue Fever: An Observation of a Tertiary Care Centre

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Abstract

Objectives: Cases of dengue are on the rise and India experienced its worst epidemic during 2015. There was almost a 2 times rise in the number of cases. This study was done to understand the varied presentation and manifestation of dengue at a tertiary care centre of Haryana, India.

Methods: This was an observational cross sectional study undertaken at PGIMS Rohtak, Haryana, India. One hundred and one patients aged $\geq$ 14 years, who had positive test results for dengue, as NS1/IgM, were included in the study. Clinical presentations, haematological, and biochemical markers were studied and analyzed.

Results: Out of 101 patients, 63.3% were males. Overall, 95% had fever followed by headache (62.3%), rash (53.4%), retrorbital pain (43.5%), and abdomenal pain (43.5%). Furthermore, 31.8% of patients had bleeding manifestation, of which the commonest was petechiae (12.8%) followed by malena (7.9%) and bleeding gum (6.9%). All patients had raised liver enzymes. Platelet count of < 50,000/mm^3 was present in 79.2%. Leucopenia was found in 43.5% of patients. Ultrasonography suggestive of free fluid was found in 44.5%. Hypokalemia was seen in 21.7% of patients. Complications, such as acute respiratory distress syndrome (ARDS) and DIC, were seen in 2.9% and 5.9% cases. Overall mortality rate was 2.97%.

Conclusions: Dengue could have varied presentations ranging from a simple febrile illness to fatal multiorgan failure. It is crucial to understand the features, which predict the progress of dengue fever (DF) to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Considering that the treatment of dengue is relatively simple, early institution of appropriate therapy with close monitoring of vital signs and laboratory parameters could help prevent morbidity and mortality related to dengue.

Keywords: Dengue Fever, Hypokalemia, Petechiae, Leukopenia

1. Background

Dengue is a mosquito-borne viral disease, which is caused by dengue virus that belongs to the family Flaviviridae and has 4 serotypes. Mosquitoes of the genus Aedes, principally Aedes aegypti, are responsible for its spread. During the last 3 decades, incidence has risen dramatically with increasing geographic expansion to new areas and in the present decade, from urban to rural settings. Approximately 50 million dengue infections occur every year and around 2.5 billion people live in dengue endemic countries (1). While cyclic epidemics are on the rise throughout the globe, there is in-country geographic expansion occurring as well within countries like India with multiple serotypes of virus in circulation. In India, according to the national vector borne disease control programme (NVBDCP), in the year 2015 there was a total of 99913 cases of dengue with 220 deaths, which was double that of the previous years (2). Dengue has diverse clinical presentations, often with unpredictable clinical progression and outcome. Symptomatic dengue virus infections could be grouped into undifferentiated fever, dengue fever (DF), and dengue haemorrhagic fever (DHF). Dengue haemorrhagic fever is further classified to 4 severity grades, with grades III and IV being defined as dengue shock syndrome (DSS) and expanded dengue syndrome (3). While the majority of patients recover well from a minor clinical course, a few progress to severe disease, which is characterized by plasma leakage with or without haemorrhage. It is difficult to predict the progression of non-severe cases to severe disease. However, this is of utmost importance since apt treat-

ment may avert these patients from development of severe disease. For a disease that is perplexing in its presentation, management is relatively easy and very effective in saving lives as long as it is provided on time. The key is awareness and understanding of the clinical features of the different phases of the disease, which would enable a balanced approach to case management and good outcome. For a country like India that tackles the epidemic of dengue every year, there is a large financial burden on the government as well as patients. Therefore, understanding the varied presentation and disease burden of dengue in India is essential to assist policy makers and public health managers to prepare for control of outbreaks. With the background of this very fact and dramatic increase in the number of cases from previous year with more atypical presentation, there is a need to relook at clinical and biochemical spectrum of dengue fever. Hence, this study was planned to demonstrate the clinical and laboratory parameters of serologically confirmed cases of dengue fever.

2. Methods

This observational cross sectional study was performed from 20th of May 2015 to 20th of October 2015 at a government educational hospital. This hospital catered mostly referral cases from all across Haryana and adjoining states of the country. Rohtak city, in which the study was conducted, has a population of 10 lacs with a gender ratio of 868 females for every 1000 males. The climate is hot semi arid and the economy of the city is mainly based on agriculture. Patients aged $\geq$ 14 years, who referred to the emergency department with symptoms suggestive of tropical fever were screened. A total of 710 patients were screened and 110 patients were confirmed to have dengue with NS1 antigen and/or IgM dengue antibody positivity by using the dengue diagnostic kit (SD BIOLINE Dengue Duo combo device). Nine cases with other concomitant illnesses, such as malaria, typhoid, leptospirosis, scrub typhus, and tuberculosis, which was confirmed by laboratory tests, were excluded from the study. Finally, statistical analysis was performed on 101 patients. Detailed history regarding symptoms was obtained. Subjects were thoroughly examined and clinical variables were measured by the same resident and senior resident under the supervision of a faculty member to avoid bias. Serologically confirmed dengue patients were subjected to clinical case definition and disease severity was classified to DF, DHF, and DSS, according to the world health organization (WHO) criteria (3). A complete haemogram, renal/liver function tests, chest X-ray, electrocardiogram (ECG), abdominal Ultrasound (USG), and thorax were also done.

2.1. Ethics Statement

The study was analyzed and approved by the ethics committee review board of PGIMS Rohtak. Informed consent was obtained from each patient.

2.2. Statistical Analysis

Analyses were performed using the SPSS software, Version 20. Total numbers and percentages were calculated for different categorical variables, such as clinical features and biochemical parameters.

3. Results

Out of 101 confirmed cases, 63.3% were males. Most of the patients in study group were from the district Rohtak and its surrounding districts i.e. Jhajjar and Bahadurgarh. The majority of cases were from the age group of 21 to 60 years old (Table 1). As shown in Table 2, fever was the commonest presentation being present in 95% of patients and average duration of fever was 3 to 5 days. The next common symptom at presentation was headache, which was present in around 63%. Other common clinical features were rashes (54%), pain in the abdomen (42.5%), and retro orbital pain (43.5%). Around 35.6% of patients had pruritus, which was observed to occur during the later stages of febrile period along with improvement of platelet count. A total of 32 (31.6%) patients had bleeding manifestation, of which petechiae (12.8%) and malena (7.9%) were the most commen (Table 3). Furthermore, DF was observed in 40.9% while DHF (grade I and II) and DSS (DHF grade III and IV) were observed in 51.4% and 7.7% of cases, respectively. Clinically, hepatomegaly was present in 25.7% of patients and splenomegaly in 20.7%. Free fluid could be demonstrated in 12.8% and pleural effusion in 9.9%. A total of 7 (6.9%) patients had SBP $<$ 90 mmHg and they responded with adequate oral and intravenous fluids. A total of 6 (5.9%) patients had features suggestive of DIC and 3 (2.9%) patients were diagnosed to have ARDS. Total mortality was 3 (2.9%). The remaining patients had good recovery with time.

As shown in Table 4, the majority of the patients (79.2%) had platelet of $<$ 50,000 cells/mm^3 at presentation. At presentation haemoglobin of $>$ 16 gm% was present in 25.7% and haematocrit $>$ 45% in 23.4%. Overall, 43.56% of patients had evidence of leucopenia TLC being less than 4000 cells/mm^3. Liver function test derangement was universal. Hypokalemia was found in a total of 22 patients (18.8%), out of which 3 patients had symptomatic hypokalemia with weakness of bilateral lower limbs and absent deep tendon reflexes. On ultrasonography of abdomen and thorax and chest X-ray, more than one-third of cases had evidence of serositis.

Table 1. Gender and Age Characteristics

Variables	Value			
Age	14 - 20	21 - 40	41 - 60	> 60
Male	12	25	21	6
Female	9	12	11	4
Total	21	37	33	10

Table 2. Clinical Features

Clinical Features	No of Patients	Percentage, %	Clinical Features	No of Patients	Percentage, %
Fever	96	95	Pleural effusion	10	9.9
Headache	63	62.3	SBP < 90 mmHg	7	6.9
Rash	54	53.4	Breathlessness	6	5.9
Retro orbital pain	44	43.5	DIC	6	5.9
Pain abdomen	44	43.5	ARDS	3	2.9
Conjunctival suffusion	40	39.6	Pruritus	36	35.6
Positive tourniquet test	33	32.6	Nausea and vomiting	29	28.7
Hepatomegaly	26	25.7	Splenomegaly	21	20.7
Ascitis	13	12.8			

Table 3. Bleeding Manifestations

Bleeding Tendencies	No of Patients	Percentage
Petechiae	13	12.8
Epistaxis	6	5.9
Haemtemesis	5	4.9
Malena	8	7.9
Bleeding gum	7	6.9
Haemptysis	2	1.9
Haematuria	1	0.9
Menorrhagia	3	2.9

4. Discussion

Dengue has become a major public health concern across the globe with the virus expanding its presence at an alarming rate. Due to climatic changes and failure to control mosquito vector, there is increased frequency of epidemics. Easy availability of diagnostic kits along with alertness among medical fraternity has led to increased number of cases being detected. There is also a rise in various atypical manifestations and severity of dengue fever. As per new classification of WHO, dengue is classified to severe dengue, dengue with warning signs, and dengue without warning signs (4). Early danger signs of dengue, such as abdominal pain, recurrent vomiting, hepatomegaly, increased haematocrit, and clue of fluid leak should be monitored carefully for timely action to prevent severe complications.

The current study demonstrates the varied clinical profile and laboratory parameters of dengue fever. There was a greater number of male patients in the current study (63.3%) as compared to females, which may be because of the proportion of male population being higher in the study area. On analysis of collected data, it was shown that fever (95%) was the most common presenting symptom, which was similar to other studies in India (5-7). Headache and retrorbital pain were seen in the majority of cases. Conjunctival injection was found in 39.6% and rash in 53.4% of cases. Patients in the group with rash and conjuctival injection were the ones with features of DHF. Kumar et al. (8) in their study documented that headache was present in 47.6% and rash in 21.7% of patients. Other than the above-mentioned symptoms, gastrointestinal symptoms were more prevalent, of which abdominal pain was present in 42.5% and nausea/vomiting in 28.7% of the study population. Liver injury due to dengue virus could be responsible for such symptoms. Nimmagadda et al. (9) also demonstrated similar findings in their study. Fever presented with gastrointestinal symptoms is a common finding of various other febrile illnesses like typhoid and lep-

Table 4. Lab Parameters

Parameters	No of Patients	Percentage
AST > 40 U/L	100	99
ALT > 40 U/L	101	100
ASTT> 3 times normal	48	47.5
ALT> 3 times normal	78	77.2
ALP > 117U/L	23	22.7
Thrombocytopenia, cells/mm^3		
< 50,000	80	79.2
> 50,000 - 1 lac	21	20.7
Haemoglobin > 16 gm%	26	25.7
TLC < 4000 mm^3	44	43.5
HCT > 45%	22	23.4
Hypokalemia, mEq/L		
3.5 - 2.5	19	18.8
< 2.5	3	2.9
Creatnine > 1.5 mg/dL	3	2.9
Urea > 40 mg/dL	10	9.9
GB thick walled	30	29.7
USG free fuid	45	44.5
Blunted CP angle on Chest X-ray	15	14.8

tospirosis, which are prevalent in India and they may delay the diagnosis of dengue. The current study suggests that dengue must be included in the differential diagnosis of patients with fever and gastrointestinal symptoms.

Hypotension was recorded in 6.9%, they responded well to fluids. Itching was noticed in 35.6% of the cases, mostly during the period in which platelets were on the rise, this is in contrary to other studies barring a few. Rachel et al. (6) from their study in Kollam, Kerala documented pruritis in 10.4% of their patients and Deshwal et al, (10) showed this disease in 13.4% of patients. This is thought to be due to the interaction of the virus with the host cells causing release of different chemical mediators and initiation of immunological mechanisms.

Bleeding manifestations have been a known feature of DF and currently a common manifestation because of low platelet count and efflux from blood vessels. Other factors, which may be responsible, are immune mediated disorders, bone marrow suppression, and aggregation of platelets to endothelium cells. In the current study, the researchers found that 32.6% of patients had positive torniquet test while 31.6% of patients had bleeding episodes in the form of petechiae (12.8%) and malena (7.9%). The current study showed a positive correlation between positive tourniquet test and bleeding tendency, which was in contrary to the other previous studies (11). Eight patients (7.9%) had spontaneous bleeding as their initial presenting complaint in the current study group. Therefore, in case of outbreak of dengue fever, one should be careful that bleeding could only be the sole presentation without other associated typical features of dengue fever. During the current study, patients who had bleeding manifestation were not universally found to have platelet of < 20,000 cells/mm^3. Even patients, who had platelet count of > 50,000 cells/mm^3 were found to have bleeding manifestations. Various other studies across India showed that although thrombocytopenia is a common finding in dengue patients, there is poor correlation between bleeding tendencies and platelet count (10, 12-14). Virus-induced inhibition and destruction of myeloid progenitor cells could lead to low leukocyte count. The researchers found that only 43.5% of cases had a leukocyte count below 4000 cells/mm^3. However, in the study of Itoda et al. (11), leucopenia was detected in 71% of cases, while Ageep AK et al. (15), reported leucopenia in 90%. However, Mittal H et al. (14) found leucopenia only in 19.2% of cases. Patients with leucopenia along with severe thrombocytopenia in the study group were the ones, who had major episode of bleeding and shock.

Hypokalemia is a well-known electrolyte imbalance of dengue fever. Overall, 21.7% of patients had hypokalemia in the current study group and 3 (2.97%) had symptomatic hypokalemia with bilateral weakness of lower limbs and absent deep tendon reflexes. These findings are consistent with other studies (16). The proposed mechanisms are entry of potassium to the cells or transient renal tubular disturbance, which causes increased urinary potassium wasting. Stress of infection causes adrenergic surge and secondary insulin release could result in intracellular shift of potassium and hypokalemia (17). Therefore, patients presenting absent tendon reflexes and weakness of lower limbs mimicking Guillain-Barre syndrome, before proceeding further dengue, should be ruled out.

Dengue virus via interaction with host cells causes release of various cytokines and stimulates immunologic mechanism, vascular endothelial changes, infiltration of mononuclear cells, and perivascular edema (18). Ascites, pleural effusion, and gall bladder edema from capillary leak syndrome are one of those features. The researchers found that clinically free fluid was demonstrated in 12.8% and pleural effusion in 9.9%, yet on ultrasonography, 44.5% patient had free fluid in the abdomen, 29.7% had gall bladder edema, and 14.8% had evidence of pleural effusion. Ultrasonography is highly sensitive in detecting even small amounts of pleural effusion and ascites. Ultrasonography could detect plasma leakage in various body compart-

ments of the body. Ultrasonographic signs suggestive of plasma leakage were evident before significant changes in hematocrits occurred. Therefore, during an epidemic, the ultrasonographic findings suggestive of gallbladder (GB) edema with or without collection of free fluid in other areas in a febrile patient should indicate towards the possibility of DF/DHF.

Hepatic dysfunction is familiar in dengue infection yet the degree of liver dysfunction varies in intensity from mild elevation of transaminases to severe injury with jaundice. The researchers found that 100% of cases had some degree of hepatic impairment in the form of raised liver enzymes. However, when calculated for more than 3 times of normal for 47.5% raised ALT and 77.2% had raised AST. In a study by Nimmaggada et al. (9) it was shown that raised liver enzymes were seen in 92.6% of cases. Overall, 92.7% of patients had Aspartate Transaminase (AST) > 40 U/L and three-fold increase was seen in 58.7%. Furthermore, 85.3% of patients had alanine transaminase (ALT) > 40 U/L and three-fold increase was seen in 38.7% of cases. Varieties of renal disorders have been linked with dengue. Acute renal failure could complicate severe dengue infection and carries a high mortality rate. In this study, 2.97% of patients had creatinine > 1.5 mg/dL. DIC was detected by clinical parameters and supported by laboratory parameters and occurred in 5.9% of cases, out of which, 5 patients survived. Severe thrombocytopenia was noted in all the cases associated with DIC. 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. Early restoration of adequate tissue perfusion is critical to prevent progression of dengue shock syndrome to ARDS. However, equal care must be exercised to avoid excessive fluid infusion after adequate volume replacement because fluid overload may result in ARDS. Pulmonary haemorrhage is another fatal complication to watch out for in these patients (19). The researchers had 3 patients, who went into ARDS, out of which 2 patients had poor outcome and 1 recovered. Patients with bleeding tendency, platelet of < 20,000 cells/mm^3, leukopenia, and raised haematocrit were the ones, who had one major complication, such as DIC or ARDS. Mortality rate in the current study group was 2.9%, which was similar with South-East Asian countries. Increased mortality rates were shown in other studies and could be due to reinfection and late presentation to the hospital. The current data is suggestive of significantly different clinical and laboratory parameters of DF and DHF. Dengue fever could be self limiting yet DHF could be calamitous and a highly morbid disease causing systemic dysfunction. The current need is to predict the development of DHF/DSS, which would provide information to identify individuals at higher risk and give sufficient time to clinicians for reducing dengue-related morbidity and mortality. Lee et al. in their study tried to derive a score to predict the severity of dengue using simple parameters, which are easily available and measurable. Simple severe dengue risk score could assist clinicians in deciding which dengue patients need hospitalization, and may thereby improve clinical practice by decreasing the number of unnecessary hospitalizations and by reducing mortality and morbidity, particularly in resource-limited countries (20).

There were a few limitations in the current study. The cohort included mainly patients from Haryana and neighbouring state while India is a large country with diverse geographical condition across the country, and different regions could have different ranges of severity of dengue. The researchers also did not include patients below 14 years of age. Despite these limitations, this study also had several strengths. The hospital was a tertiary care centre, to which more patients with severe dengue referred. The researchers screened and excluded patients with co-infections to avoid bias in observation of features of dengue.

4.1. Conclusion

Dengue viral infection is a dangerous threat to global health. India is facing a dengue crisis every year and death due to dengue has risen to an alarmingly high rate. Dengue is a highly unspecific illness, which could have varied presentation and atypical manifestations. This study demonstrates and supports various other studies indicating that early diagnosis and suspicion could lead to improved outcome. As dengue is complex in presentation yet easier to treat, strict vigilance along with symptomatic treatment and adequate hydration is all that is required for recovery.

Footnotes

Statement of Authorship: All authors gave approval to the final version submitted.

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