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ORIGINAL ARTICLE

Clinical Spectrum and Laboratory Profile of Patients with Dengue Fever in a Tertiary Care Centre of Eastern UP, India- An Observational Study

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Abstract

Introduction: Dengue fever is mosquito born seasonal viral illness. There is increasing burden of dengue in India. Seeing the increasing number of cases and epidemics worldwide, WHO reclassified dengue classification in 2009. There has been very few studies of dengue fever based on new classification system and especially from this part of country, so we did a study of clinical spectrum and laboratory profile of dengue fever patients according to WHO classification 2009. **Methods:** A prospective observational study, was carried out in Sir Sundar Lal hospital, Institute of medical sciences, Banaras Hindu University, Varanasi, after ethical approval from ethical committee of institute and taking proper consent from patients. Patients with incomplete follow up and records were excluded. Daily evolution of sign and symptoms, warning signs, postural fall of blood pressure were recorded. Suspected cases were considered as case of dengue fever based on the result of rapid diagnostic kit method. Laboratory profile like complete blood count, haematocrit, liver and renal function test, PT/INR (prothrombin time), activated partial thromboplastin time (aPTT), chest x-ray, electrocardiography (ECG) and ultrasonography (USG) abdomen and chest were documented. **Results:** Out of 99 patients of dengue fever, 15.2% were of dengue without warning sign, 72.7% were of dengue with warning sign, and 12.1% were of severe dengue. Plasma leakage was clinically detectable in 10% case while on ultrasonography it was present in 40.4% cases. Postural fall of blood pressure was present in 30% cases and was present earlier than rise in haematocrit in all cases. Mucosal bleeding was present in 12% cases (n=12) and most of them were minor bleeding. In 97% cases serum glutamic oxaloacetic transaminase (SGOT) was elevated more than serum glutamic pyruvic transaminase (SGPT), PT/INR was normal in all and aPTT>41 seconds was associated with risk of bleeding. Some cases had atypical manifestations like relative bradycardia (3%), transient eosinophilia (3%), hypokalemic paralysis (2%). **Conclusion:** Most cases of dengue fever are of non-severe dengue with mucosal bleeding present in small proportion of patients and that too of minor variety. There is no correlation between bleeding manifestation and platelet count. Fluid leakage is present in good number of patients which is more evident sonographically. Our

study showed that measurement of postural fall of blood pressure has potential to become early and important bedside clinical surrogate marker for detection of fluid leakage. More studies with large sample size is required to validate it.

Dengue fever is a mosquitoes borne viral disease caused by positive-stranded encapsulated RNA virus belonging to the *flavivirus* genus of the *Flaviviridae* family and transmitted by *Aedes* mosquitoes, mainly by Aedes *aegypti*. A recent study done at the University of Oxford has estimated that India had the largest number of dengue cases, with about 33 million apparent and another 100 million asymptomatic infections occurring annually[1]. Rapid urbanisation and mixing of human populations by transport has helped in maintenance of endemicity. Dengue has a wide spectrum of clinical manifestations, often with unpredictable clinical evolution and outcome. While most patients recover following self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without haemorrhage. Dengue fever is characterised by three phases in continuum as febrile phase, generally lasting for 2 to 7 days, followed by critical phase of short duration in which maximum complications like fluid leakage and organ damage occurs and lastly recovery phase in which there is risk of volume overload because of over hydration[2].

Earlier in 1997, WHO classified it as dengue fever and dengue haemorrhagic fever which was further classified into 4 grades of which grades 3 and 4 constituting dengue shock syndrome. This classification system led to confusion and controversies, as most of patients having feature of plasma leakage or shock didn't bleed, while some patient bled in absence of shock and it was difficult to classify otherwise normal patients with isolated platelet count below 1 lakh/μl, so WHO reclassified it in 2009 as dengue fever with or without warning signs and severe dengue which is more apt for triage of patients, patient management point of view, epidemiological surveillance and important tool for endpoint measurement of clinical trials[3].

In our study, we have tried to study clinical spectrum of dengue fever in the context of new WHO classification system.

METHODS

A prospective observational study was carried out in suspected dengue fever patients, attending Medicine outpatient department (OPD) and/or admitted in Medicine ward at Sir Sunder Lal Hospital, BHU, Varanasi, during period from July 2013 to August 2015.

Selection of the patients: In the season of outbreak of dengue mainly during rainy season from July to October, cases of acute febrile illness with features of viral prodromes such as myalgia, headache, arthralgia, retro orbital pain or rashes were investigated for dengue fever including NS1Ag test and dengue IgM and IgG antibody test, by using standard rapid diagnostic kit method. Each suspected case was taken as a case of dengue if NS1Ag and/or dengue IgM antibody was positive[4]. Further confirmation of dengue by virus culture and PCR method was not done because of technical feasibility.

At the time of presentation cases of dengue were divided into dengue without warning sign, dengue with warning sign and severe dengue according to WHO 2009 criteria. Patients in which symptoms were mild and there were no warning signs were followed on the OPD basis with written advice to come immediately if any of the warning symptoms develops. Those patients in which only warning signs was low platelet count <100,000/μL but >50,000/μL and oral intake of fluid was sufficient and were from the local catchment area of the hospital were followed on the daily basis ,those who could not follow and patients with other warning signs like abdominal pain or tenderness, persistent vomiting, clinical signs of fluid accumulation, mucosal bleeding, lethargy and restlessness, liver enlargement, increased haematocrit and those of severe dengue (respiratory distress, severe bleeding and/or severe organ impairment) were admitted. Those patients which lost follow up, having incomplete file records and didn't give consent were excluded.

Study was carried after approval from ethical committee of IMS, Banaras Hindu University, Varanasi.

Clinical study

Evolution of clinical symptoms and signs were recorded. Daily morning and evening postural blood pressure measurement was done. Postural blood pressure was taken after 3 min of standing and considered significant when there was fall in systolic BP of ≥20 mm Hg or diastolic BP fall ≥10 mm Hg or postural tachycardia of ≥30/minute or symptoms of hypotension like unable to stand because of dizziness. Clinical assessment for fluid leakage in pleural, peritoneal, pericardial spaces, pedal oedema and bleeding was done. Patients were critically assessed for any signs of bleeding and were classified into WHO bleeding

grade 1 to 4[5]. Drug history of using non-steroidal anti-inflammatory drugs (NSAIDS), steroids or anticoagulants were documented.

Lab parameters

Haematocrit measurement was done by ABG analyser machine Cobas b 121, Roche company at the time of presentation and according to clinical status to guide fluid therapy. Daily complete blood count (CBC) with manual platelet count (MPC) and in those in which rate of fall of platelet count was rapid it was performed twice a day. Liver and renal function tests, routine microscopy of urine, stool for occult blood (when they complained of black stool), chest X-ray PA and lateral view, ultrasonography and ECG were also performed on each patients. Monitoring of coagulation parameters PT and APTT was done in our haematology laboratory to study coagulation parameters, irrespective of bleeding manifestations.

RESULTS

Total 124 patient were diagnosed with dengue fever, of which 20 patients lost follow up and 5 patients did not give consent. Among remaining 99 patients 65% were male and 35% were female. Most of the patients were from young age group, 33.3% from 11-20 yrs., 40.4% from 21-30 yrs., and 11.1% from 31-40 yrs. age groups. Most of the patients (85.9%) presented between days 3 to day 7 of illness. Clinical features at the time of presentation were as shown in table no 1.

Table no. 1: showing common sign and symptoms of dengue fever patients.

Sign and symptoms (n=99)	Percentage[%]
Myalgia	93.9
Fever	91.9
headache	80.8
Arthralgia	24.2
Retrorbital pain	26.3
Flushed skin	36.4
Rash	14.1
anorexia	66.7
Nausea	64.6
Vomiting	48.5
Diarrhoea	7.1
Cough	2
Postural fall of blood pressure	30
Relative bradycardia	3

Table no. 2: showing warning signs in the patients of dengue fever.

Warning sign	Percentage[%]
Low platelet count <100000/µl	85.3
Lethargy and restlessness	22.2
Abdominal pain and tenderness	21.2
Persistent vomiting	20.2
Fluid collection on clinical examination	10
Mucosal bleeding	12.1%
Liver enlargement >2 cm	2

Of the total 99 patients 72.7% had warning signs as shown in table no 2. Severe dengue was present in 12.1% patients at the time of presentation. Respiratory distress was present in 8.1% cases, shock in 3% case, severe bleeding in the form of hematemesis and melena was present in 1% and severe organ involvement in the form of raised liver enzymes > 1000 IU/dl in 1%.

By 7th day of illness, 90.2% of the patient became afebrile. Fever persisted for 8 days, 9 days, 10 days, 12 days, 15 and 22 days in 1%, 1%, 2%, 3%, 1% and 1% patients respectively. In these patients other common infectious and iatrogenic causes were ruled out. Prolongation of fever was associated with severity of liver involvement in 3% cases. Two patients had dengue associated hypokalemic paralysis which improved after intravenous potassium supplementation.

Serological markers

Only NS1Ag was positive in 60.6% and both NS1Ag and IgM were positive in 23.2%, all NS1Ag, IgM, IgG in 9% and only IgM in 7% of cases.

Complete blood count

Most common and early abnormality in complete blood count was decrease in total leucocyte count which preceded fall in platelet count. During initial part of dengue fever there was leucopenia which gradually returned to normal after 5 or 6 days.

28.2% cases had relative lymphocytosis at presentation and it was eventually present in total 62% cases during course of disease. There was eosinophilia in 3% cases. On retrospective examination there was no eosinophilia in immediate previous report and also it gradually normalised in follow up without any specific treatment.

Decrease in platelet count started after 3 days and reached their nadir value on day 7 with mean value of 69.02±8.32/

µl after which it started to rise again. Similarly maximum increase in haematocrit was on day 6 with mean value of 52.60 ±4.31%.

Table no. 3: showing relation between haematocrit and postural fall of blood pressure.

	Postural fall present(n=30)	Postural fall absent (n=69)	p-value
Day 0	41.30±6.64	38.20±7.65	0.074
Day 1	43.31±5.65	39.98±7.28	0.088
Day 2	44.62±9.99	39.17±5.77	0.079
Day 3	46.52±10.46	40.21±10.23	0.259
Day 4	51.35±0.91	41.74±10.67	0.235
Day 5	44.83±5.34	40.17±8.017	0.390

Postural fall of blood pressure was present in 30% of the patients. Mean haematocrit in the patients which had postural fall in blood pressure was higher as compared to the patients in which there was no postural fall but difference between two groups was not significant. Table no. 3 shows the mean haematocrit in those which had postural fall and those who had no postural fall and their corresponding P value since the day of admission taking it as day 0.

Bleeding manifestation

Of total 99 patients, WHO grade 1 bleeding manifestation was present in 20%, of which rash constituted major part i.e. 16%, rest part was constituted by per vaginal bleeding (just spotting), gum bleeding <30 min, subconjunctival bleeding and epistaxis <30 min,1% each. Grade 2 bleeding was present in 6% cases which was constituted by macroscopic haematuria in 2% and haemoptysis, hematochezia and oropharyngeal bleeding >30 minute, 1% each. Grade 3 bleeding was present in 1% in the form of melena requiring blood transfusion, which had history of prolonged shock. Grade 4 bleeding was present in 1%, in the form of fatal hematemesis and melena causing death having history of NSAIDS intake for body ache.

Relationship between platelet count and mucosal bleeding

There was bleeding in 33% of patients in each platelets range group, i.e. those having nadir platelet counts ≤ 10,000/µl and those in which nadir platelet counts were >150 $\times 10^3$/µl. There was no bleeding in those having nadir platelet counts between 11-20$\times 10^3$/µl. 16.2%, 3.84% and 8.3% patients showed bleeding manifestations belonging to platelet range groups 21-50, 51-100, 101-150$\times 10^3$/µl, respectively. Thus showing no relationship between platelet count and bleeding manifestation. Brief description of bleeding in different platelets range groups is shown in table no. 4.

Table no. 4: showing bleeding manifestations and its relationship with platelet count.

Nadir MPC range (1×10^3/µl)	(n=99)/%	Mucosal bleeding (n/%)	Brief description
≤10	3 (3%)	1(33%)	Haemoptysis, grade 2
11-20	18(18%)	0(0%)	No bleeding
21-50	37(37%)	6(16.2%)	Epistaxis<30 min, pv bleed just spotting, subconjunctival haemorrhage all grade 1, hematochezia, tonsillar bleed >30 min both grade 2, fatal melena grade 4.
51-100	26(26%)	1(3.84%)	Melena grade 3.
101-150	12(12.1%)	1(8.3%)	Per vaginal bleeding more than spotting, grade 2
≥151	3(3%)	1(33%)	Haematuria grade 2

Regarding liver enzymes, SGOT had mean value of 268.32±79.07 IU/L and was elevated more than SGPT which had mean value 147.79±31.24 IU/L. In one case SGOT was elevated up to 7600 IU/L and SGPT up to 6400 IU/L. In only 3% case SGPT was elevated more than SGOT. Total bilirubin was elevated mildly in 5% cases, with predominant elevation in direct bilirubin fraction. Abnormalities in liver function test normalised in all patients after follow up of 1 month.

In 3% cases creatinine and urea were mildly elevated. Mean value of creatinine was 1.04±.43 mg/dl and mean value of urea was 42±24.71 mg/dl.

Those patients who had abdominal pain and tenderness (n=22), in all of them amylase and lipase level were studied. Amylase level was well within normal range with mean value 51.12±10.38 U/L. There was mild elevation in lipase level with mean value 63.50±38.21 U/L, but always <3 times the upper normal value.

Table no. 5: Showing relation between aPTT and bleeding manifestation.

aPTT (seconds)	Bleeding manifestations		Total
	Present n/%)	Absent (n/%)	
<36	6 (14.6%)	35 (85.3%)	41
36-40	3 (33.3%)	6 (66.6%)	9
41-45	6 (54.5%)	5 (45.4%)	11
46-50	4(100%)	0 (0%)	4
51-55	3 (75%)	1 (25%)	4
>55	1 (100%)	0 (0%)	1

Coagulation parameters

Coagulation parameters were studied over 70 patients, as rest 29 patient either didn't give consent or lost follow up. In most of the patients PT/INR was within normal range with reference value <1.3 of INR. We divided results of aPTT in 5 different ranges. Table no. 5 shows corresponding percentage value of bleeding manifestations in different range groups. When we applied chi-square test, P value was significant <.001 in the 1st group <36 seconds, while in rest of groups it was not significant as the total number (n) was low. Subsequently we made two groups <41 second and >41 seconds, then prolongation in APTT >41 seconds was found to be significantly associated with bleeding risk with P value <.001, as shown in table no. 6. Disseminated intravascular coagulation (DIC) was present in 41.4% of the patients which was mostly mild grade but severe in 7.1% cases.

Table no. 6: showing relation between aPTT >41 seconds and bleeding.

aPTT	Bleeding manifestations		total
	Present	absent	
<41 seconds	9(18%)	41(82%)	50
>41 second	14(70%)	6(30%)	20

Serositis

It was present in 10% cases on clinical examination but on ultrasonography evidence of serositis was present in 40.4% cases. Gallbladder wall oedema in 37.7%, pleural effusion in 34.3% and ascites in 26.2% cases.

Final diagnosis and outcome

Out of 99 patients 15.2% (n=15) were of dengue without warning signs, 72.7% (n=72) were of dengue with warning sign and 12.1% (n=12) were of severe dengue, of which 2 patients expired, one had hematemesis and melena with refractory shock, with history of NSAIDS intake for body ache. His manual platelet count was 42,000/µl, SGOT 258 IU/dl, SGPT 112 IU/dl, INR 1.2, and a PTT was >51 seconds. Second patient who expired had prolonged shock leading to multiple organ dysfunction. She developed acute respiratory distress syndrome and her manual platelet count was 1 lakh/µl, SGOT 116 IU/dl, SGPT 96 IU/dl, INR 1.1, aPTT > 36 seconds, creatinine 2.8 mg/dl, urea 53 mg/dl.

DISCUSSION

In our study males were more in number (65%). The probable reason could be that they are more involved in outdoor activities and females generally wear clothes covering most part of the body. Most of the affected patients were of young age group. Only 6% patients were older than 50 yrs. This may be because of higher dispersion and mobility in younger age group. Our findings were in accordance with other studies like Gupta *et al.*[6] and Bandyopadhyay B *et al.*[7].

Table no. 7 tells about the common symptoms in our study as compared to other studies. Higher reporting of flushed skin in study of Singapore may be because people are more fair coloured in Singapore than India. Difference in percentage of rash may be attributed to different strains of dengue viruses.

Table no. 7: symptoms frequency and its comparison with previous studies

	Our study	P Babaliche and D Doshi in 2015,[8] (India)	Low. JGH *et al.*, in 2011,[9] (Singapore)
Flushed skin	36.2%	40%	80%
Rash	14.4%	36%	9.6%
Arthralgia	26.2%	31%	60.8%
Retrorbital pain	24.2%	--	26%
Mucosal bleeding	7.1%	22%	5.6%

One of the characteristic feature was presence of anorexia 66.7%, nausea 64% and vomiting 48.5% cases, while in the above study of Singapore they were present in 81.2%, 50% and 16.4% cases respectively. Presence of nausea, vomiting, and in some cases persistent vomiting, associated with abdominal pain and tenderness, all causing poor oral intake in the background of dengue pathophysiology causing

plasma leakage making the patient prone to low intravascular volume and shock.

Regarding unusual manifestations of dengue there were 2 patient of dengue associated hypokalemic paralysis. R.K Garg *et al.,* 2013 have shown the dengue as second most common cause of secondary hypokalemic paralysis after thyrotoxicosis[10]. Jitendra Ingole and Ramesh S. S *et al.* have shown relative bradycardia in 39% and 61% cases respectively, but in our study it was present in 3% cases[11,12]. This difference may be due to difference in strains of dengue virus.

Recent researches about dengue have shown that fluid leakage is more important pathophysiology than bleeding, so we sought to measure postural fall of blood pressure as a bedside clinical surrogate marker of fluid leakage and postural fall of blood pressure was present in 25% of the patients in our study at the time of presentation and in 30% cases throughout the course. We further analysed correlation between the postural fall in blood pressure and haematocrit value. We found that those patient in which there was postural fall of BP had mean value of haematocrit higher than those in which there was no postural fall of BP, but the difference between mean of two values of haematocrit level was not significant. Michels. M, *et al.* have found that single haematocrit value is not helpful in discriminating between patients with and without ultrasonographic evidence of fluid leakage. They also have mentioned that even change in haematocrit value is not helpful as hemoconcentration was first observed in 62% cases after the critical phase when the patient already started to recover[13].

Common abnormality in complete blood count was leucopenia with relative lymphocytosis. Wells. R. A *et al.* have also described lymphocytosis with presence of atypical lymphocytes in acute dengue and eosinophilia in convalescent phase[14]. Thrombocytopenia was most common finding in 85.3% cases. Ageep AK *et al.,* Mittal H *et al.* and Seema A *et al.* also showed thrombocytopenia was a most common laboratory finding, observed in 88%, 92.6% and 84% cases respectively[15,16,17].

Trung DT *et al.,* have shown liver enzyme derangement more in SGOT than SGPT in 97% cases clinically visible jaundice in 2% cases which was similar to finding of our study[18]. In our study SGOT was elevated more than SGPT in 97% cases, and was generally below 500 IU/dl except in 4 cases in which it was above 500 IU/dl. Only 5% cases had elevation in their serum bilirubin level with predominant direct fraction elevation.

Our study showed no correlation between platelet count and bleeding manifestations, suggesting that platelet count is not the sole determinant of bleeding in case of dengue patients. This was consistent with the findings of Lye DC *et al.,*[19] and Lum LC *et al.,*[20].

Most of patients had normal PT/INR value with INR being below the reference range <1.3. Coagulopathy in the form aPTT >41 seconds was associated with increased bleeding risk and present in 28.75% cases. Our findings were quite similar with the results of study done by Kannan A *et al.,*[21]. They have shown prolongation in APTT >41 seconds in 22.3% cases with normal INR values in study over 264 patients of dengue fever.

DIC was present in 41.4% cases which was mild grade mostly except in 7.1%, it was severe. Funahara. Y *et al.* have shown that there is mild degree of DIC in 56% of non-shock patients of dengue and it can be severe if shock is prolonged[22].

Major limitation of our study was that we did not confirm the cases of dengue fever by virus culture or Polymerase chain reaction (PCR) method.

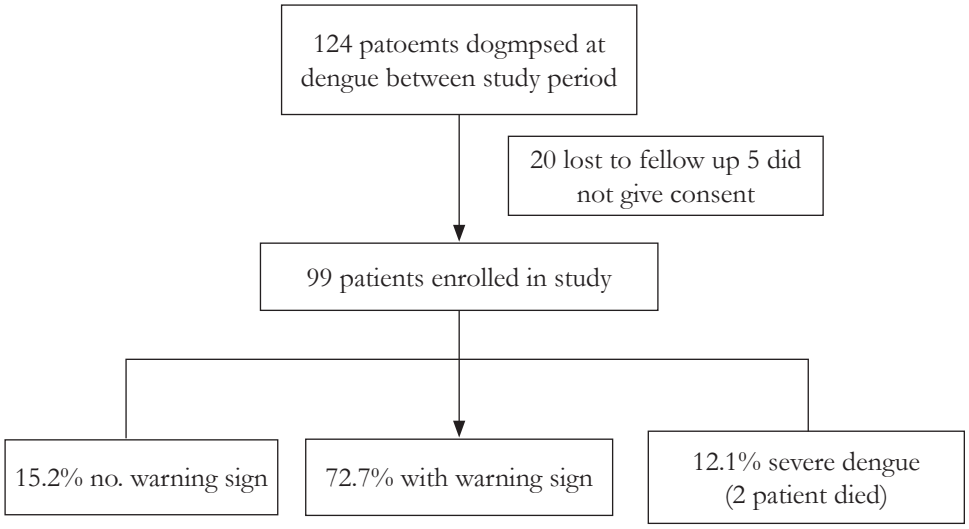

Figure 1

So, we found that mucosal bleedings are present in small proportion of patients and usually of minor grade, if severe bleeding is present then other causes like NSAIDS intake, prolonged shock should be looked for. Most have features of plasma leakage which is less evident on clinical examination but more so on ultrasonographic examination.

Measurement of postural fall of blood pressure has potential to become important clinical bedside surrogate marker of plasma leakage, but this needs to be validated by study on larger sample size.

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