

Original Research Article

Capillary Leak Syndrome in Hospitalized cases of Dengue Fever - Is it really a marker of severity?

Abstract

Background: Dengue is a mosquito-borne viral infection spread by the *Aedes aegypti* mosquito and is caused by one of the four dengue viruses of *arbovirus* family. Infection gives lifelong immunity against that viral serotype. A person can get infected with all four viruses in a lifetime. WHO has acknowledged that the global incidence of dengue has grown dramatically in recent decades, and that about half of the world's population is now at risk. It is commonly believed that subsequent infection with another serotype of dengue virus increases the risk of Dengue Hemorrhagic Fever (DHF) and 'Dengue Shock Syndrome' (DSS). The endothelium is the target organ in severe dengue and capillary leak syndrome (CLS) is the main complication of severe dengue. **Material and Methods:** The present study was done at Narayana Multispeciality hospital, Jaipur and had been approved by the institute ethical committee. It is a four year observational study comprising of 164 indoor patients of confirmed DF who had CLS. The presenting symptoms, dengue NS1 antigen and antibody tests, co-infection, co-morbidities, laboratory investigation, mortality, duration of hospital stay were recorded, tabulated and analysed. **Results:** Besides fever, hepato-splenomegaly, chills, vomiting, abdominal pain, body-ache, and bleeding manifestations, isolated gall bladder (GB) wall edema was present in 26(15.9%) cases, ascites in 8(4.9%) cases, and pleural effusion in 11(6.7%) cases respectively. Pleural effusion was right sided in 8(4.9%) cases, bilateral in 3(1.8%) cases and only left sided in none of the cases. Both ascites and pleural effusion was present in 9(5.5%) cases and triad of ascites, GB wall edema and pleural effusion was seen in 76(46.3%) cases respectively. None of the case had pericardial effusion. **Conclusion:** We conclude that all hospitalized patients of DF with thrombocytopenia and transaminitis should be evaluated early by ultrasonography for evidence of CLS. Hemoconcentration and hypoproteinemia are not sensitive tools to pick up capillary leakage in clinical practice and ultrasonography better identify patients at risk of developing severe dengue. It can pick subclinical plasma leakage early and presence of an edematous gallbladder wall in these patients merits intensive monitoring for development of complications. The Probable pathogenesis of DHF or DSS which is considered due to immune mediated platelet destruction with release of cytokines and activation of the complement system leading to capillary

leak syndrome needs to be **relooked**. This is the largest case series of 164 cases of CLS in hospitalized DF cases.

Keywords: Dengue fever; Pleural effusion; Gall bladder wall edema; Ascites; Capillary leak syndrome.

Introduction

Dengue is a complex disease. After the incubation period which ranges from 3-14 days, the illness begins abruptly and in patients with moderate to severe disease, is followed by three phases- febrile, critical and recovery. During the transition from the febrile to afebrile phase which lasts for 2-7 days, patients without an increase in capillary permeability will improve without going through the critical phase. On the other hand patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. This period of clinically significant plasma leakage usually lasts 24 to 48 hours. Also the degree of plasma leakage varies from patient to patient with severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress, it being considered as the marker of severity for severe dengue.

Capillary leak syndrome (CLS) broadly is characterized by hypotension with hemoconcentration, hypoalbuminemia without albuminuria and generalized edema. The etiology is multiple and it can be primary idiopathic systemic capillary leak syndrome (ISCLS) or secondary capillary leak syndrome due to various causes including venomous snake bite (ophitoxemia), viral hemorrhagic fever (dengue, hanta virus), toxins (abrin, ricin, sanguinarine), certain drug reaction (interleukin-2, interferon beta1b, gemcitabine), endocrine disorders (hypothyroidism), Sepsis, and others (following cardio-pulmonary bypass, BMT). However, in dengue fever elevated hematocrit, pleural or other effusion and low proteins is considered as an enough evidence of plasma leakage caused by increased vascular permeability. Generalized edema is not a feature.

There are not many articles in literature on CLS in DF. CLS is the principal pathologic event in causation of DHF and dengue shock syndrome (DSS). The WHO definition has retained capillary leakage as the defining lesion of most cases of severe dengue infection. The hematocrit in CLS in DF is usually $> 40\%$, but may be as high as 55-60%. The need to have area specific cut off values has been suggested and studies from Delhi and Chennai recommended such values ^(1, 2). We have taken a cut off 37.5% in our patients since we do not have our own area

specific cut off⁽¹⁾. This hemoconcentration is due to plasma leakage, beginning at the end of the febrile stage and continues for one to two days after defervescence of fever. Early diagnosis of CLS is thus essential to start volume replacement and indicates progression to DSS.

We present and discuss here the findings in 164 cases of CLS in hospitalized cases of DF seen by us between January 2013 to December 2016 in our institution in Jaipur (Rajasthan). The fluid accumulation seen involved both abdomen and pleural cavity. Further, the fluid rapidly clears in a week's time without any specific treatment. Prognosis in CLS, in general, depends on the underlying etiology and mortality is low in dengue fever. There were only three mortality in these 164 cases of CLS in DF.

Material and Methods

The study was done in our tertiary care center. Our institutional ethics committee approved this retrospective study and informed consent was not required. The study is a four year retrospective observational study of 164 indoor patients of confirmed DF with features of CLS and was conducted in the department of internal medicine, Narayana Multispeciality Hospital, Jaipur (Rajasthan). All these patients had critical phase of DF. Medical case record files of these cases of DF with CLS, in medical unit 1, between January 2013 to December 2016 were collected from medical records department (MRD). Demographic data, symptomatology, features of CLS, co-morbidities, co-infections, complications, dengue test report, routine laboratory investigations, ultrasonography, X-ray chest, in addition to blood and blood product transfusions and mortality data were collected, tabulated and analyzed.

Laboratory diagnosis methods available for diagnosing dengue virus infection are usually by detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. In present study diagnosis of dengue fever was done on the basis of dengue NS1 antigen and antibodies (IgM / IgG) test reports (done by dengue solid phase immune-chromatographic rapid test kits for qualitative detection). Primary dengue fever (pDF) was diagnosed in cases who had either positive NS1 antigen or IgM antibodies or both. Secondary dengue fever (sDF) was diagnosed if subject had a positive NS1 antigen or IgM antibodies along with IgG antibodies or presence of all three (NS1 antigen, IgM antibody and IgG antibody). All patients given a diagnosis of DF were routinely followed-up for capillary leakage and other complications by physical examination and laboratory tests (including a complete blood count, chemistry panel and

ultrasonography of abdomen, pleural cavities and pericardial space) on admission and repeated as required afterwards .

All ultrasound examinations were performed in fasting state (minimum of six hours fasting) with an ultrasound machine (GE GE Logic P6 model) using 3.5 MHz and 5 MHz probes. Gallbladder (GB) wall thickness >3 mm as measured on ultrasound were identified as positive for GB wall edema .Thoracic scanning for bilateral pleural cavities and pericardial space was done in either sitting or supine posture. Liver measuring more than 15 cm was taken as hepatomegaly and spleen measuring more than 12 cm was taken as splenomegaly. Radiographic evidence of capillary leakage was considered to be present if either of ascites, unilateral or bilateral pleural effusion ,pericardial effusion or a thickened edematous gallbladder were present.

Results

The typical clinical manifestations of dengue infection range from self-limited dengue fever (DF) to dengue hemorrhagic fever (DHF) with shock syndrome. In all indoor medical record of 264 indoor cases of DF were screened. All these patients had been routinely followed up for capillary leakage by Thoraco-abdominal ultrasonography and other complications by physical examination, laboratory tests, x-ray and a chemistry panel on admission and repeated as needed afterwards. 164 cases had features of CLS. Our results indicate that CLS is not uncommon in hospitalized cases of DF, being present in 164 (62.1%) cases. All these 164 cases of CLS were then further analyzed. There were 107 (65.2%) males and 57 (34.8%) females .The median age was 25 years in males and 31 years in females, and the female-male ratio was 1:1.9 (Table 1). The youngest and the eldest patient were of 13 years and 82 years respectively

The result of serology tests for dengue fever (NS1, IgM, IgG antibody) are shown in table 2. pDF was seen in 133(81.1%) and sDF in 31(18.9%) cases. The clinical manifestations are mentioned in table 3. Fever was present in almost all cases (97.6%). Other feature were hepatomegaly (65.2%), chills (54.3%) vomiting (50%) abdominal pain (53%), body-ache (41.5%), nausea (39.6%) and splenomegaly (30.5%). Headache (23.2%), bleeding manifestation (16.5%), cough (9.8%), diarrhea (11.6%), rashes (11.6%) and itching (7.9%) were not very common. Hematocrit more than 37.5% was seen in 103(62.8%) cases (table 4). Only 11(6.7%) cases had hematocrit of $>50\%$. Hypoalbuminemia was seen in 75 (45.7%) cases (table 4).It was moderate to severe in 59(36%) cases. Transaminitis –raised aspartate transaminase(AST) was seen in 160(97.6%) cases and alanine transaminase (ALT) in 145(88.4%) cases respectively.(table 4).

Thrombocytopenia was present in all cases (table 5). Mild thrombocytopenia was present in 9(8%), moderate in 10(6.1%) and severe in 145(88.4%) cases. Bleeding manifestation were present in 27 (16.5%) cases, menorrhagia being the commonest. Therapeutic platelet transfusion were given in only 23(14%) of these cases who had associated significant bleeding manifestation. Lowest platelet count was $3 \times 10^3/\text{cmm}$. Severe critical thrombocytopenia ($<20 \times 10^3/\text{cmm}$) was seen in 96(58.5%) cases.

Site of plasma leakage in these 164 cases is mentioned in table 6. Polyserositis (ascites, GB wall edema and right sided or bilateral pleural effusion) was seen in 76(46.3%) cases. Isolated GB wall edema was seen in 26(15.9%), ascites and pleural effusion in 22(13.4%) and isolated left or bilateral pleural effusion in 11(6.7%) cases respectively. None of the cases had only left side pleural effusion or pericardial effusion.

Table 7 shows co-morbidities, co-infection, MICU admissions and mortality in these 164 cases. Co-morbidities such as diabetes mellitus, hypertension, coronary artery disease, COPD, benign prostate hyperplasia requiring indwelling catheterization were seen in 24(14.6%). Co-infection was seen in 07(4.3%) cases. It was Scrub typhus in 4 cases, plasmodium vivax malaria in 1 case and plasmodium falciparum malaria in 2 cases respectively. MICU admissions were required in 28(17.1%) cases. There were 3(1.8%) mortality. All of them had primary dengue fever (NS1 antigen positive). First one is an elderly 70 years male, post CABG case and had fever along with soakage/bleeding from surgical site in fifth week after surgery. He had thrombocytopenia, hypotension, adult respiratory distress syndrome, acute kidney injury, severe transaminitis (AST 8400 IU/L and ALT 5329 IU/L) along with features of CLS. Another case was of a 40 years female who presented with fever and pain abdomen. She had biochemical and ultrasound evidence of acute pancreatitis, transaminitis, hemoconcentration and thrombocytopenia with lowest platelet count of $11 \times 10^3/\text{cmm}$. She had sudden death after 10 hours of admission. The family refused for autopsy. The third patient was a 25 year male who also had fever with pain abdomen. He had acute pancreatitis, severe transaminitis (AST 150 IU/L, ALT 6838 IU/L), mild jaundice, bleeding (melena), thrombocytopenia and CLS. All three of them were given blood and blood products transfusion as needed. Rest of the patients had a favourable course.

It was observed that cases with secondary sDF 31(18.9%) were not more symptomatic than pDF cases. The 3 mortalities seen in this study had pDF. The



average hospital stay duration was 4-6 days (table 8). 152(92%) cases had a stay of less than a week.

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203 DISCUSSION

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205 Dengue virus infection ranges from a mild febrile illness to severe illness. Severe
 206 dengue is mainly characterized by transient plasma leakage, which may lead to a
 207 sudden onset of shock around the end of febrile phase of illness. Severe bleeding
 208 and organ impairment as compared to CLS are less common features of severe
 209 dengue. The capillary leakage is considered to be present if any of the following
 210 three features are present: (1) a rise in the hematocrit equal to or greater than 20%
 211 above average for age, sex and population;(2) a drop in the hematocrit following
 212 volume replacement treatment equal to or greater than 20% of baseline; and (3)
 213 signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia^(4,5).
 214 Of these, hemo-concentration is a retrospective parameter and rarely of clinical
 215 benefit. Hypoalbuminemia is not seen frequently and clinical recognition of
 216 plasma leakage is a difficult sign. Thus,clinically it becomes difficult to predict
 217 which dengue patient will develop severe complications. In our case series a
 218 hematocrit of >40 was seen in 81 (49.4%) cases and when area specific cut off
 219 value (37.5%) is taken into consideration the number rises to 103(62.8%) as was
 220 done in a Chennai based study⁽¹⁾. Unfortunately we did not have any area specific
 221 cut off from this part of the country and for our study we have considered the value
 222 from Chennai based study. Hypoalbuminemia (< 3.2gm/dl) was seen in 75(45.7%)
 223 cases suggesting that it is an infrequent finding. In contrast, ultrasonography can
 224 directly visualize plasma leakage and thoraco -abdominal ultrasonography is a
 225 highly accurate method for assessing even small amounts of pleural effusion,
 226 ascites,pericardial effusion and GB wall edema. It has a sensitivity of nearly 100%
 227 and is even recommended by the 2009 WHO guidelines as a suitable tool for
 228 assessing CLS^(6,7,8). Thus ,instead of a rise in hematocrit and hypoalbuminemia ,
 229 thoraco-abdominal ultrasonography is an important tool to pick up CLS early in
 230 adult dengue fever patients. It picked up 164 cases among 264 cases of DENF.

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232 The most recent WHO classification (2009) defines severe dengue infection in case
 233 plasma leakage leading to shock or respiratory failure, severe bleeding or severe
 234 organ failure is present . However, as seen in this study also ,in clinical practice
 235 severe bleeding and severe organ failure are relatively uncommon and rarely occur
 236 without plasma leakage.Hence, plasma leakage is an essential element of severe
 237 dengue, regardless of any classification. Various studies have demonstrated that
 238 among hospitalized patients with uncomplicated DF, the prevalence of sonographic
 239 capillary leak ranges from 34%^(7,8) to as high as 100 %⁽⁴⁾ .It was 62.1% in our

series of 264 DF cases. Our study has some limitations. Ours being a tertiary centre selection bias is expected as usually severe cases are being referred to such centres. Serial ultrasounds were not done from the first day of infection in these patients as most of them were referred cases and the first ultrasound was done within 24 hours of admission. We cannot comment on the the day of illness at which plasma leakage could have started. Nevertheless our results have reproduced a high prevalence of capillary leakage in hospitalized adult patients during critical phase of DF.

In our case series, CLS was found in 68.9% of cases (31 of 45) with sDF and 75.2% of cases (133 of 219) with pDF. The mechanism that underlies capillary leakage in DF remains undefined. VEGF, a potent permeability enhancing cytokine, has been thought to play a pivotal role in mediating plasma leakage in DHF. Another mechanism is antibody dependent enhancement i.e., immune enhancement of viral replication because of previous exposure to dengue virus as a cause of capillary leakage/severe disease. Studies in travelers from non endemic countries have shown that capillary leak is more likely to represent a fundamental mechanism of disease in DEN-V infection, regardless of the host immune status. Meltzer et al suggested that secondary infection is not a prerequisite condition for development of capillary leak in dengue infection and does not increase the risk for severe disease among travelers with dengue infection.⁽⁷⁾

In our case series CLS among subjects with primary infection was seen in significant number of cases. The importance of immune enhancement caused by secondary infection as the only cause of capillary leakage in DF needs to be relooked. It is possible that CLS may even be a universal finding at microscopic level⁽⁷⁾. It appears that several factors including pathogenicity of specific viral serotype, virulence of the circulating virus, immunological responses, higher levels of viral loads and NS1 proteins, VEGF and other cytokines are all implicated in a complex manner for the appearance of CLS/DHF cases with DF.

In CLS collection of fluid frequently involves multiple sites. In our series polyserositis (GB wall edema + ascites + pleural effusions) was seen in 76(46.3%) cases, followed by GB wall edema in 26(15.9%) cases, and ascites + GB wall edema in 22(13.4%) cases respectively. None of the cases had left side pleural effusion or pericardial effusion. The similar findings were noted in others studies also^(9, 10). The fluid accumulation was mild to moderate in our case series and none of our cases required aspiration. It cleared within a week's time and no specific treatment was required.

Scrub typhus and malaria co infection with dengue fever has been reported in many studies^(11, 12, 13). We had 7 (4.3%) cases with dual infection and all of them recovered. 4 of them had co infection with scrub typhus. Malaria co infection was seen in 3 cases. Two of them had plasmodium falciparum and one plasmodium vivax co-infection respectively. One of these case also developed secondary hemophagocytic lymphohistiocytosis syndrome. Persistence of fever, moderate to severe transaminitis with cholestasis, presence of an eschar, multi-organ involvement should caution clinician to suspect co-infection.

Little is known about dengue in the elderly⁽¹⁵⁾. A surveillance study⁽¹⁶⁾ showed that clinical manifestations of dengue in the elderly are similar to those of younger adults. In our case series we had 10 cases of DENF in elderly (>60 years age). Of them 6 cases had CLS and did not differ from other cases in their clinical manifestations and outcomes. Only one of them who had undergone CABG and had multiple co morbidities died following severe DHF.

Conclusions:

1. One of the most important challenges for clinicians who see dengue patients is to identify patients who will progress to severe disease. In absence of accurate biomarkers, presence of plasma leakage can pick up such cases early in critical phase.

2. Hematocrit is determined by tracking changes in serial haematocrit measurements and hypoalbuminemia is infrequent. Both are insensitive indicators of CLS compared to ultrasonography.

3. Ultrasonography can help to identify dengue patients at risk for shock and that patients with ultrasonographic evidence of plasma leakage should be monitored more carefully for circulatory status.

4. We have presented clinical profile of 164 cases of DF with CLS. Thrombocytopenia and Transaminitis were seen in almost all cases. We suggest early ultrasonography for CLS in hospitalized patients (and even if not admitted) who have these two laboratory features. Bleeding manifestations and organ dysfunction is not very common.

5. Capillary leakage is seen in both primary as well as secondary dengue infection. We did not see secondary dengue infection being more severe than primary dengue infection.

6. Have a high index of suspicion for co-infection in cases with inadequate or failure of therapeutic response.

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Conflict of interest: Nil.

Ethical committee approval :Done.

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TABLE 1

NUMBER OF CASES WITH AGE GROUP

S. NO.	Age Category	No. of Male Cases	No. of Female Cases	Total	Percentage
1	0-10	0	00	00	00
2	16 -20	25	12	37	22.6
3	21-30	48	14	62	37.8
4	31-40	19	16	35	21.3
5	41-50	10	06	16	9.8
6	51-60	04	04	08	4.9
7	61-70	01	03	04	2.4
8	71-80	00	01	01	0.60
9	81-90	00	01	01	0.60
10	91-100	00	00	00	0.60
		107	57	164	

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Table 2

DENGUE SEROLOGY RESULTS

Type of dengue fever	Antigen/Antibody Detected	Number Of Cases		Total
		Male	Female	
Primary dengue	NS1 only	85	38	123
	IgM only	02	02	04
	NS1+IgM	04	02	06
	Total			133(81.1%)
Secondary dengue	NS1+IgG	07	05	12
	IgG and IgM	04	02	06
	NS1, IgM ,IgG	05	08	13
	Total			31(18.9%)

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Table 3.
DISTRIBUTION OF DENGUE CASES WITH CLS ACCORDING TO CLINICAL
MANIFESTATION

Clinical Manifestations	No. of cases(%)
Fever	160(97.6)
Hepatomegaly	107(65.2)
Chill	89(54.3)
Vomiting	82(50.0)
Abdominal Pain	87(53.0)
Body-ache	68(41.5)
Nausea	65(39.6)
Splenomegaly	50(30.5)
Weakness	34(20.7)
Loss of Appetite	28(17.1)
Headache	38(23.2)
Bleeding	27(16.5)
Diarrhea	19(11.6)
Cough	16(9.8)
Rashes	19(11.6)
Itching	13(7.9)

Table 4.Hematocrit, Albumin and Transaminases

Hematocrit(%)		Hypoalbuminemia(mg/dl)		AST / SGOT(IU)		ALT / SGPT(IU)	
Test value	No. of cases(%)	Test value (Normal ≥ 3.3)	No. of cases(%)	Test Value	No. of cases(%)	Test Value	No. of cases(%)
37.5-40.0	22(13.4%)	3.2-3.0 (mild)	13(7.9%)	38-74 (1-2 XULN)	5(3%)	66-130 (1-2 XULN)	55(33.5%)
40.1-50.0	70(42.7%)	2.9-2.5 (moderate)	46(28%)	75-185 (2-5X ULN)	53(32.3%)	131-325 (2-5X ULN)	73(44.5%)
50.1-60.0	11(6.7%)	< 2.5 (severe)	16(9.8%)	≥ 186 (>5XULN)	102(62.2%)	≥ 326 (>5XULN)	17(10.4%)

AST/SGOT:Aspartate transaminase serum glutamic-oxaloacetic transaminase

ALT/SGPTAlanine transaminase/Serum glutamic pyruvic transaminase

Table 5. Thrombocytopenia, Hemorrhage, and Platelet transfusions

Platelet count ($\times 10^3/\text{cmm}$)	Total cases (n=164)	Bleeding cases	Therapeutic transfusions	Prophylactic Transfusion
<20	96	18	18	47
20 – 50	49	08	04	08
50 -100	10	01	01	00
100-150	09	0	00	00

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405 Table No. 6: Site of capillary leak

Site of capillary leak	No. of cases(%) (n=164)
Ascites + GB wall edema + Pleural effusion	76(46.3)
Only GB wall edema	26(15.9%)
Ascites + GB wall edema	22(13.4)
Ascites + Pleural effusion	09(5.5)
Only Ascites	08(4.9)
Isolated Right side pleural effusion	08(4.9)
Bilateral pleural effusion	03(1.8)

406 GB: Gall bladder

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Table No. 7: Incidence of co-morbidity, co-infection, MICU admission and mortality in CLS dengue cases (n=164)

	Male	Female	Total(%)
Co-morbidity	17	07	24(14.6)
Co-infection	04	03	07(4.3)
MICU admission	20	08	28(17.1)
Mortality	02	01	03(1.8)

Table 8

Hospital stay duration.

Duration of stay in hospital in days	No. of cases(%)
1-3 days	44(26.8)
4-6 days	107(65.2)
7-9 days	10(6.1)
10-12 days	2(1.2)
13-15 days	1(0.6)
Total Patients	164