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Original Article

Incidence of Plasma Leakage in Dengue Hemorrhagic Fever

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Abstract

Background: Dengue is still existing as an important threat to child health. This virus induces wide spectrum of clinical conditions including dengue hemorrhagic fever (DHF), characterized by plasma leakage and bleeding, which is often life endangering. Dengue is showing a recent upsurge in Bangladesh when Covid 19 is threating huge number of human lives.

Objective: Plasma leakage is the key feature of serious DHF. Early clinical suspicion, establishment of diagnosis of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) and proper therapeutic intervention are crucial for saving lives. This study is undertaken to see the severity nature of Dengue infection in our territory.

Methods & Materials: Eighty one admitted children in the Paediatric ward of DNMI H, had been suffering from various dengue infection were included in study. Diagnosis was made by history taking, clinical features and supporting investigative findings like Leukopaenia, Thrombocytopaenia and haematocrit (raised or not), NS1 antigen positivity, Dengue antibodies (IgM & IgG) and Radiological & sonographic evaluation of the Chest and Abdomen.

Result: 43 children (53%) were male and 38 (43%) female. The age range was from 06 months to 13 years. Fifty eight (71.60%) were urban and the remaining 23 (28.40%) were from rural areas. Chief complaints were fever with unusual weakness. Temperature recorded were 100F to 103F except in 02 cases in whom fever remitted before admission. Other important symptoms were Headache and rarely Haemorrhagic manifestations. Thrombocytpaenia found in all cases and Leukopaenia in 56 (69.14%) children. Haematocrit were raised (>10%) in 9 patients only.

Features of plasma leakage (Pleural effusion /Ascites / Bleeding sign) found in 09 children those have raised haematocrit. Among all children 78 recovered, 03 cases (01 with uncontrolled gastrointestinal hemorrhage and 02 with breathing difficulty demanding ICU support) were referred to better center.

Conclusion: Ultrasonographic signs and changes in hematocrits are useful tools for detecting plasma leakage in dengue infection. Pleural effusions and ascites are common features. With careful therapeutic intervention patients improve rapidly but should be monitored closely as leakage may continue for couple of days.

Key words: Plasma leakage, Dengue hemorrhagic fever, Pleural effusion in dengue.

Introduction

Dengue is remaining an important health issue worldwide. Dengue viruses, a group of four serologically distinct viruses belonging to genus Flavirus, are the cause of this serious viral diseases. This viral infections induces wide spectrum of clinical conditions including dengue hemorrhagic fever (DHF), a haemorrhagic disease characterized by plasma leakage and bleeding. The common feature of DHF is a transient period of plasma leakage and a hemorrhagic episode. This occurs mostly during a secondary dengue infection. WHO reported significant increase in dengue cases, from approximately 900 cases per year in 1950's & 1960's decade to about 500,000 cases every year in 1990's decade.[1] It is endemic in Southeast Asia and South America, causes significant morbidity, mortality, and economic burden. In Indian subcontinent and Oceania, dengue is emerging as most important viral infectious diseases.[2,3]

Aedes aegypti is the principal mosquito vector in virus

transmission.[4] The genome of dengue virus encodes 10 different gene products: C (capsid), prM (matrix), E (envelope) and nonstructural proteins including NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.[5] NS1 is the only nonstructural protein with a soluble form that can be detected in circulation.[6]

Most primary infections in children are usually clinically unnoticeable but some patients may manifest undifferentiated fever. Primary infections in older children and adults are likely to produce characteristic dengue fever (DF), a febrile illness along with non-specific symptoms like headache, retro-orbital pain, myalgia and occasionally hemorrhagic manifestations.[7] A small portion of patients develop dengue hemorrhagic fever (DHF), the most serious form of disease. The hallmark of DHF is the plasma leakage which may lead to the loss of intravascular fluid volume and circulatory insufficiency. Bleeding is another feature of severe disease. Bleeding may occur in both DF and DHF, but more severe bleeding, specially bleeding from the gastrointestinal tract, is found more frequently in DHF. Raised level of liver enzymes and thrombocytopenia are found in both DF and DHF patients but are more severe in DHF. Evidence of plasma leakage are the presence of pleural and/or ascitic fluid or hemoconcentration.[7] DHF patients who have narrow pulse pressure (less than 20 mmHg) or show signs of shock are classified as dengue shock syndrome (DSS). Other severe clinical manifestations including hepatic failure and encephalopathy have been reported in dengue cases.[8-10]

Dengue is showing a recent upsurge in Bangladesh when Covid 19 is threating huge number of human lives in mid-2021. This study is undertaken to see the severity nature of Dengue infection in our territory.

Methods & Materials

Eight one admitted children in the Paediatric ward of DNMI H from April to September, 2019, suffering from various dengue infection were included in this study after obtaining informed consent from parents. Diagnosis was made on basis of history, clinical features and supporting investigations like CBC to see Leukopaenia & Thrombocytopaenia (Platelet count < 100,000 cell/cu mm) and haematocrit (raised or not), NS1 antigen positivity , Dengue antibodies (IgM & IgG), Radiological & Sonographic evaluation of the Chest and Abdomen. Patients suffering from other diseases like enteric fever along with dengue diseases were not included.

Apethetic child DHF

Picture showing rash in the leg skin

Result

Total number of cases included in this study were 81, among them 43 (53%) were male and 38 (43%) female. The age range was from 06 months to 13 years. Fifty eight (71.60%) were urban and the remaining 23 (28.40%) were from rural areas. Out of them 79 (97.43%) were immunized as per our country schedule .Only two child, aging 06 months and 09 months had not been completed their schedule at that time.

Table-I: (n = 81)

Age & sex distribution according to age group.

Age	Male	Female	Total
< 01 year	01	02	03 (3.70%)
< 05 years	12	09	21 (25.93%)
< 10 years	22	17	39 (48.19%)
< 15 years	08	10	18 (22.22%)

The main complaints were fever with unusual weakness. Duration of fever ranges from 02 days to 07 days. Temparature recorded at the time of admission were 100F to 103F except in two cases in whom fever remitted before admission. Other associated symptoms were headache, myalgia and / or arthralgia, rash and rarely haemorrhagic manifestations.

Table-II: (n= 81)

Presenting symptoms

Fever	79 (97.53%)
Headache	23 (28.40%)
Myalgia & Arthralgia	19 (23.46%)
Rash	13 (16.04%)
Haemorrhagic manifestations	04 (4.94%)

The investigations done after admission were CBC, Haematocrit, NS1 antigen test, Chest X-ray, USG of the chest & abdomen and also Dengue antibodies (IgG & IgM) in demanding cases.

Table-III: (n=81)
Blood picture at presentation

Thrombocytopaenia	<100000 cells per mm^3 in 47 cases	< 50000 cells per mm^3 34 cases
Leukopaenia	Present in 56 patients	Absent in 25 patients
Haematocrit	Raised (>10%) in 9 patients	Not raised in 72 patients

Features of Plasma leakage found in 09 children. Both the ascitic patients had associated pleural effusion also. Two patients with bleeding manifestation had concomitant pleural effusion.

Table-IV: (n=9)
Features of Plasma leakage

Nature of leakage	Number of patients
Pleural effusion	09
Ascites	02
Bleeding sign	02

NS1 antigen test were done in all the cases . Out of them 74 cases were positive, 04 weakly positive and the rest 03 children were negative. Immunoglobulin (IgM) were advised in some cases particularly those were NS1 negative and weakly positive. Features of Plasma leakage found in 09 children. Both the ascitic patients had associated pleural effusion also.

Among these children 78 recovered , 03 cases (01 with uncontrolled gastrointestinal hemorrhage and 02 with breathing difficulty demanding ICU support) were referred to better center.

Discussion

Dengue fever is caused by the dengue virus. Symptoms usually starts 03 to 07 days after getting infected. Generally recovery occur in the following 02 to 07 days. In a small fraction of cases, the disease continue for longer period and may turn into a more severe form, Dengue hemorrhagic fever, manifested by haemorrhage, thrombocytopenia and /or plasma leakage, and in some case into a more dangerous form i.e. Dengue shock syndrome, where blood pressure decrease sharply.[11] Aedes aegypti virus has five serotypes.[12,13] Infection with one type generally offers lifelong immunity to that particular type, but a short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications.[14]

Plasma leakage means the protein rich, fluid component of the blood starts leaking from blood vessels into the surrounding tissue. Pleural effusion and/or ascites usually become clinically evident. This is a serious complication that distinguishes dengue haemorrhagic fever from common dengue fever. Plasma leakage may begin to appear when fever begins to disappear.[15]

In our study out of 81 children 09 cases develop signs of plasma leakage, pleural effusion in all the 09 cases and ascites in 02 patients. Both the ascitic patients had simultaneous pleural effusion also. Time of our first clinical suspicion were variable, from 3rd to 5th days after the onset of fever. Vascular leakage usually becomes evident 3–6 days after the onset of illness, and known as the critical phase[16] Dengue fever may progress through three distinct clinical phases, the febrile phase, the critical phase and the recovery phase.[17] After being infected there may be an initial incubation period of 3-7 days, followed by sudden onset of high fever, related to high viraemia, which is termed as febrile phase.[17] Some patients may proceed to critical phase manifested by features of plasma leakage, lasting for 24–48 hours while others progress to recovery phase directly.[18] WHO suggested three dengue clinical phases based on the days of onset of illness, febrile phase/viremic phase (day(s) (1-3), critical phase (days 4-6) and recovery phase (days>7). But this does not happen always, prolonged febrile phase may be followed by the recovery phase, sometimes the febrile and critical phases may overlap each other. Plasma leakage is the hallmark of critical phase, if there is no evidence plasma leakage, the case is considered as prolonged febrile illness.[19]

Clinical suspicion had arisen when the usual symptoms were more pronounced along with newer complaints like breathing difficulty, right lower chest pain, enlarged tender liver and/or bleeding signs. etc. To confirm following investigations were done e.g. Chest X-ray P/A and Rt. Lateral view, Ultrasongraphy of the Chest and Abdomen and also Haematocrit to detect haemoconcentration. Sonography appeared to be more sensitive than radiology as chest X-ray could detect only in 03 (33.33 %) cases where as USG could do it in 08 patients (88.89%) developed pleural effusion in our study. Pleural effusion is the most common ultrasonographic sign of plasma leakage (62%). Thickening of the gallbladder wall and ascites were detected less frequently (43% and 52% respectively).[20] Researches using Chest X-rays and serial USG of the chest and abdomen to detect plasma leakage have demonstrated that progressive and significant accumulation of fluid only occurred in a subset of dengue cases.[20,21]

Bleeding were present in 02 cases, one epistaxis the other with haematemesis. Both had concomitant

pleural effusion. Haematocrit assessment is another indirect evidence of plasma leakage. Sudden drop in platelet count and rising haematocrit (>10%), are haematological markers for the progression of plasma leakage.[22] Haematocrit was not statistically significant between febrile phase and critical phase but significant in the group of plasma leakers.[23] In our series all the 09 cases platelet count were below 50000 per cubic mm and significantly raised haematocrit values (>10%) were found in eight patients (88.89%) among the plasma leakers. DHF is usually accompanying with a transient upsurge in vascular permeability because of endothelial dysfunction in critical phase. Increase vascular permeability is concomitant with vascular leakage and subsequent accumulation of fluid in pleural and peritoneal cavities, and with reduced blood pressure, pulse pressure and poor organ perfusion.[24]

Among all these eighty one children seventy eight recovered including 06 babies of plasma leaker group by medication only. Three children (01 with uncontrolled gastrointestinal hemorrhage and 02 with breathing difficulty demanding ICU support) were referred to better center.

All the patients plasma leakage were managed by Isotonic intravenous fluids and colloids infusion to replace plasma, but carefully monitored, because unnecessary fluid infusion may precipitate pulmonary edema and respiratory failure. In our series 06 patients out nine improved satisfactorily. Close monitoring should be maintained as leakage may continue for next couple of days.

Conclusion

Ultrasonographic signs of plasma leakage and changes in hematocrits are useful tool for detecting plasma leakage in dengue infection. Pleural effusions and ascites give rise to respiratory problems. Severe plasma leakage can lead to hypovolemic shock. Isotonic intravenous fluids and colloids are administered to replace plasma, but the amount must be carefully monitored because too much IV fluid may precipitate pulmonary edema and respiratory failure. Patients can improve rapidly but should be monitored closely as leakage may continue for couple of days.

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