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# "CLINICAL PROFILE AND PREDICTORS OF ILLNESS SEVERITY IN CHILDREN WITH DENGUE FEVER"

Paediatrics

**Dr Manoj Kumar Ram** Senior Resident, Deptt of Pediatrics, A.N.M.M.C.H, Gaya, Bihar.

**Dr Bankey Bihari Singh*** Associate Professor & HOD, Deptt of Pediatrics, A.N.M.M.C.H, Gaya, Bihar.
*Corresponding Author

## ABSTRACT

**BACKGROUND & OBJECTIVES:** Dengue illness has become exceedingly common over the last few years globally. Due to their unique characteristics, incidence as well as mortality is higher in pediatric population as compared to adults. This study was undertaken to study clinical pattern of dengue fever in children and to identify factors predicting a more severe disease. **METHODS:** We conducted this hospital based prospective study at A.N.M.M.C.H, Gaya, Bihar over 2 years from January 2016- December 2017. Children >1 month and <15 years age with fever ≥ 3 days and symptoms suggestive of Dengue infection were included and evaluated for dengue infection by testing for NS1 antigen, IgM and IgG against Dengue infection. Children were classified into 3 clinical groups: Dengue without warning signs (DWWS), Dengue with warning signs (DWS) and severe Dengue (SD) as per WHO classification. Clinical and laboratory parameters were compared in the 3 groups. **RESULTS:** 114 children with Dengue were studied. 62 (54.4%) were males as compared to 52 (45.6%) females. 41 (36%) had DWWS, 53 (46.5%) had DWS and 20 (17.5%) had SD. Mean age was 74.1 months (SD 18.2 months) and mean weight was 21.4 kg (S.D 5.1 kg). Common symptoms were fever (100%), myalgia (76.6%), chills (62.3%), nausea/ vomiting (63.2%) and rash (53.5%). Common signs were flushed appearance (36.8%), positive Hess test (27.2%), bleeding manifestation (13.2%) and hypotension (36.8%). Laboratory investigations revealed anaemia (18.4%), thrombocytopenia (81.6%), Leucopenia (69.3%), elevated transaminase (41.2%), abnormal RFT (5.3%). 27.1% had prolonged aPTT while 21% had prolonged PT. Nausea/vomiting, bleeding, oliguria, capillary leak and liver enlargement (>2 cm) were significantly more common in severe dengue ($p<0.05$) whereas rash was commoner in non severe dengue. Lab parameters significantly more common in SD included rising hematocrit, falling platelets, high urea/creatinine/ALT and hypoalbuminemia & hypocholesterolemia. **CONCLUSIONS:** DF affects children irrespective of age. Symptoms more common in SD were nausea/vomiting, bleeding and decreased urine. Signs commoner in SD were features of capillary leak and hepatomegaly (>2 cm). Rising hematocrit, falling platelets, high urea, creatinine and ALT but hypoalbuminemia and low cholesterol were found to be statistically significant laboratory parameters associated with SD.

## KEYWORDS

Clinical Features, Complications, Dengue Fever, Dengue With Warning Signs, Severe Dengue

## I. INTRODUCTION:

Dengue illness has become exceedingly common over the last few years globally.[1] It is also the commonest arboviral disease in humans.[2] However, till early 20th century it was considered to be a febrile illness with only mild severity. It was only by 1950s that a more severe form of the illness appeared in many South-East Asian countries as an epidemic where afflicted patients exhibited two potentially life threatening complications; bleeding diathesis and shock. Hence, two new terms came into existence for this disease: Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[3] Dengue virus comprises five serotypes, DENV-1, DENV-2, DENV-3, DENV-4 and DENV-5, which are transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes.

Dengue fever has become an endemic disease in more than 100 countries. In our country, this disease is endemic in 29 states, both rural and urban area according to the annual report of the Department of Health and Family Welfare 2016-17[4]. It is estimated that around 500 million dengue cases occur globally every year of which approx 1/10th cases occur in the Indian subcontinent.[5] Inadequate/delayed treatment leads to mortality as high as 20% whereas timely diagnosis and treatment cuts down this figure to 1%. [6] Due to their unique characteristics, incidence as well as mortality is higher in pediatric population as compared to adults.[7] Dengue fever is classified according to the revised WHO classification as dengue without warning signs (DWWS), dengue with warning signs (DWS), and severe dengue (SD).[8] Fortunately, majority of children suffer from milder disease and only 5–20% progress to the more severe form which is associated with significant morbidity and mortality.

Dengue infection is frequently confused with other febrile illnesses (OFI) as the clinical features are non specific. This makes precise diagnosis strikingly difficult, resulting in inefficient treatment and increased morbidity and mortality. In addition, lack of necessary laboratory facilities, particularly in rural areas, causes difficultly in discriminating dengue from OFI. Clinical features or laboratory parameters that could potentially aid in differentiation of non-severe from severe dengue might prove to be crucial in saving the life of patients. However, not many researchers have described the clinical picture of Dengue in children in northern India, especially with regard to severity grading as per latest WHO classification. There is no general agreement on many of the presumed prognostic factors determining the clinical outcome of critically ill patients with dengue fever. With this background we intended to study in detail various parameters of children with dengue fever at our tertiary care level teaching hospital.

## II. Aim and Objectives:

**Aim:** To study the pattern of dengue fever in pediatric age group.

**Objectives:** 1. To study the clinical and laboratory parameters of dengue fever in hospitalized children.
2. To study which factors predict a more severe form of this disease

## III. Materials and Methods:

**Study setting:** Pediatrics OPD and I.P.D of Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar.

**Study duration:** 2 years, from January 2016 to December 2017.

**Study design:** hospital based prospective observational study.

**Inclusion criteria:** Children between >1 month and <15 years age with fever ≥ 3 days and symptoms suggestive of DF such as headache, nausea-vomiting, petechiae, arthralgia, and retro-orbital pain.

**Exclusion criteria:** Children with pre-existing bleeding disorder, chronic liver disease, malignancy, autoimmune and immunodeficiency disease were excluded as their clinical and laboratory parameters could mimic or influence the clinical and laboratory picture of severe dengue patients. Children who left against medical advice were excluded from the final analysis.

**Data Collection:** After obtaining written informed consent, we enrolled participants in the present study. Data was collected in structured Performa to document pertinent history and physical examination. All such children with probable Dengue infection were investigated for recent Dengue infection by testing for non-structural antigen-1 (NS-1) IgM and IgG by ELISA method. Those who tested positive were evaluated for clinical symptoms (headache,

nausea/vomiting, cough, abdominal pain, bleeding, rash), signs (decreased urine, hepatomegaly >2cm, capillary leakage), laboratory parameters (hemoglobin, hematocrit, TLC, platelets), urea, creatinine, C-reactive protein, albumin, cholesterol, ALT)) and radiological parameters (pleural effusion/ascites from chest X-ray/Ultrasonography). Based on recent WHO classification, the patients were divided into three groups - Dengue without warning signs (DWWS), Dengue with warning signs (DWS) and Severe Dengue (SD).[8] All such children were closely monitored for development of complications which were managed as per WHO guidelines.

**Statistical analysis:** The data so collected was entered in Microsoft excel and analyzed using SPSS version 20 software. Variables were presented as mean, median, percentage and standard deviations as appropriate. Chi square test or student's t test was used for testing significance of difference as applicable. *P* value less than 0.05 was considered significant.

### III. Observation and Results

Over the two year study period, 121 children were diagnosed to be suffering from Dengue at our Institute. Final analysis was done on 114 children as parents refused to participate in the study in 7 cases. 62 (54.4%) were males as compared to 52 (45.6%) females. 41 (36%) had Dengue without warning signs (DWWS), 53 (46.5%) had DWS and Severe Dengue (SD) was seen in 20 (17.5%) children. Mean age of presentation was 74.1 months (SD 18.2 months), whereas the most common age group involved was 3-9 years (approx 90% children). 9 (7.9%) children belonged to infant age group. Mean weight on admission was 21.4 kg (S.D 5.1 kg). Table1 depicts general characteristics of the participants.

**Table 1: General characteristics of children with Dengue:**

| Sl No. | Parameters | Value |
|---|---|---|
| 01 | Age in months | Mean: 74.1, SD: 18.2 |
| 02 | Weight in kg | Mean: 21.4 , SD: 5.1 |
| 03 | Male: Female | 1.2: 1 |
| 04 | Duration of fever in days | Mean: 3.9 , SD: 1.8 |
| 05 | Severity of illness | |
| | Dengue fever | 41(36%) |
| | Dengue with warning signs | 53 (46.5%) |
| | Severe Dengue | 20 (17.5%) |
| 06 | Basis of diagnosis (ELISA) | |
| | NS1 positive | 21 (18.4%) |
| | IgM positive | 27 (23.7%) |
| | Both NS1 and IgM positive | 39 (34.2%) |
| | Both IgM and IgG positive | 22 (19.3%) |
| | NS1, IgM and IgG positive | 5 ( 4.4%) |

**Symptomatology:** The most common symptom was fever in 100%, followed by myalgia in 76.6%, chills in 62.3%, nausea/ vomiting in 63.2%, rash in 53.5%, abdominal pain in 46.5%, headache in 37.7%, and arthralgia in 25.4% children.

**Signs:** Flushed appearance was seen in 36.8%, Hess test was positive in 27.2%, bleeding manifestation was seen in 13.2%, bradycardia in 13.1% and hypotension in 36.8% children.

**Laboratory parameters:** Laboratory investigations revealed anaemia (18.4%), thrombocytopenia (81.6%), Leucopenia (69.3%), relative lymphocytosis (28.9%), elevated hepatic enzymes (41.2%), abnormal RFT (5.3%), hyponatremia (23.7%), hypoalbuminemia (16.7%). 31 (27.1%) had prolonged aPTT while 24(21%) had prolonged PT. Mean values of PT, INR, and aPTT in SD were 18±3.4 sec, 1.4±0.3 sec and 44±6 sec respectively. Chest X ray showed pleural effusion in 12 cases (5 had bilateral effusion with predominant right sided involvement. 17 children had ascites. 2 children had pericardial effusion.. Table 2 shows various features of DF in severity subgroups.

**Table 2: Clinical and laboratory parameters of affected children**

| Sl no. | Parameter | DWWS (n=41) | DWS (n=53) | SD (n=20) | Total (n=114) |
|---|---|---|---|---|---|
| 01 | Rash | 31 (75.6%) | 24 (45.3%) | 6 (30%) | 61 (53.5%) |
| 02 | Nausea/vomiting | 20 (48.8%) | 35 (66%) | 17 (85%) | 72(63.2%) |
| 03 | Bleeding | 0 (0%) | 9 (17%) | 6 (30%) | 15 (13.2%) |
| 04 | Altered sensorium | 0 (0%) | 2 (3.8%) | 7 (35%) | 9 ( 7.9%) |
| 05 | Oliguria | 5 (12.2%) | 14 (26.4%) | 13 (65%) | 32 (28.1%) |
| 06 | Capillary leak | 0 (0%) | 11(20.8%) | 16 (80%) | 27 (23.7%) |
| 07 | Ascites | 0 (0%) | 9 (17%) | 8 (40%) | 17 (14.9%) |
| 08 | Pleural effusion | 0 (0%) | 5 (9.4%) | 7 (35%) | 12 (10.5%) |
| 09 | Hypotension | 5 (12.2%) | 21 (39.6%) | 16 (80%) | 42 (36.8%) |
| 10 | Liver enlargement >2 cm | 0 (0%) | 20 (37.7%) | 8 (40%) | 28 (24.6%) |
| 11 | PCV in %: Mean (SD) | 34.24 (3.56) | 37.9 (4.21) | 40.09 (5.7) | 37.34 (4.48) |
| 12 | Platelet in mm3: mean (SD) | 174231 (42397) | 122387 (55732) | 78532 (33129) | 139871(51643) |
| 13 | Urea in mg/dl: mean (SD) | 22.7 (4.1) | 27.25 (5.9) | 34.62 (7.3) | 24.68 (6.24) |
| 14 | Creatinine in mg/dl: mean (SD) | 0.43 (0.18) | 0.56 (0.22) | 0.68 (0.29) | 0.46 (0.21) |
| 15 | Cholesterol in mg/dl: mean (SD) | 122 (18) | 103 (28) | 82 (21) | 107 (24) |
| 16 | ALT in U/L: mean (SD) | 38 (8.5) | 84 (17) | 148 (59) | 42 (9.2) |
| 17 | Albumin in g/dl: mean (SD) | 4.14 (0.57) | 3.79 (0.71) | 3.12 (0.68) | 3.88 (0.73) |

(DWWS: dengue without warning signs, DWS: dengue with warning signs, SD: severe dengue)

**Features in severe vs. non-severe dengue:** In the present study we found that nausea/vomiting, bleeding, oliguria, capillary leak and liver enlargement (>2 cm) were statistically more common in SD ($p<0.05$) whereas rash was more common in non SD. We also found that thrombocytopenia did not predict the occurrence of bleeding in children. We also found that rising hematocrit, falling platelets count, high urea, creatinine and ALT, hypoalbuminemia and low cholesterol were found to be statistically significant laboratory parameters associated with SD.

**Outcome:** Mean duration of fever was 3.9±1.8 days. Mean duration of hospital stay 5.17 ± 2.613 days. Mean duration of neutropenia and thrombocytopenia were 3.6± 1.24 days and 3.8±1.38 days respectively. Interestingly we got 5 cases of dengue encephalitis in our study, all of whom improved. Mortality in the present study was 11 (9.6%) and all children who died had SD. Among them all had multi-organ dysfunction (100%) in the end and the most common underlying predisposing conditions were acute respiratory distress syndrome (36%), refractory shock (27%), intracranial bleed (0.8%), massive G.I bleeding (18%), acute hepatic failure (18%), and myocarditis (27%).

### 3. DISCUSSION:

In the present study we intended to study the profile of dengue fever in children as per latest WHO classification as well as to study factors that suggest progression to a more severe dengue. 41 (36%) had DWWS, 53 (46.5%) had DWS and SD was seen in 20 (17.5%). This is comparable to the study of Sahana and Sujatha[9] who found that 48.1% had dengue fever without warning signs, 27.2 % had DWS, and 24.7 % had SD. In the present study males were more affected with a male to female ratio of 1.27:1 as reported in most of the studies. Infants constituted 7.9% % and 65.8% children belonged to 5-10 age group which is similar to the findings of Manjunadh et al[10].

There was overlapping of clinical features between children with DWS and SD. Common symptoms in DF following fever were myalgia (76.6%), vomiting (63.2%) and abdominal pain (46.5%). Proportion of cases with vomiting and abdominal pain in the study conducted by Karoli et al[11]. was 63% and 58%. The proportion of children with headache and bleeding manifestations here was only 13.4% and 13.2%. Comparable lower incidence of bleeding and headache was reported by Kumar et al.[12]. In the study by Kassim et

al[13], 32.2% of the samples were found positive for dengue NS1 antigen, 40.9% were IgM positive, and 36.1% were IgG positive for dengue virus. Even we found that NS1 was positive in more than 50% children. This may be due to early suspicion of DF and testing in our study. Incidence of leucopenia and Thrombocytopenia was also similar to other prospective observational studies. In the present study more than 25% children had deranged coagulation profile (PT or aPTT). This observation was important because impaired fibrinolysis and coagulation are considered to be a potential pathogenic mechanism of SD. Hepatic involvement in our study is evidenced by hepatomegaly in 24.6%, elevation of hepatic transaminases in 41.2%.

In the present study we found that nausea/vomiting, bleeding, oliguria, capillary leak and liver enlargement (>2 cm) were statistically significant more common in severe dengue. Also, rising hematocrit, falling platelets count, high urea, creatinine and ALT, hypoal buminemia and low cholesterol were found to be statistically significant laboratory parameters associated with severe dengue. These findings were consistent with a recent study done in Kolkata, India.[14]

Mean duration of neutropenia and thrombocytopenia were 3.6± 1.24 days and 3.8±1.38 days respectively which is similar to the study of Mittal et al.[15] Mortality in the present study was 11 (9.6%) and all children who died had severe dengue Most of other investigators have also reported mortality in the range of 6-9%.

## 4. CONCLUSION:

Dengue fever affects children irrespective of their age; however older children are more likely to get the disease. Nausea/vomiting, bleeding, decreased urine were the symptoms more common in severe dengue. Among the sings, features of capillary leak and hepatomegaly (>2 cm) were more common in severe dengue. Also, rising hematocrit, falling platelets, high urea, creatinine and ALT, hypoalbuminemia and low cholesterol were found to be statistically significant laboratory parameters associated with SD. As severe illness is associated with a significant morbidity and mortality, early diagnosis and timely management can potentially save lives.

## 5. LIMITATION:

Ours is a single centre study and hence the prognostic markers may not be truly applicable to general population. Isolation of the virus serotypes was also not attempted. Samples for laboratory testing were sent at the time of admission, however, lab parameters change during the course of disease which was not studied.

**6. Financial disclosure:** we declare that our study has not received financial support of any sort.

**7. Conflict of Interest:** none

**Abbreviations:**ALT: Alanine transaminase; DF: Dengue fever; DWWS: Dengue without warning signs; DWS: Dengue with warning signs; SD: Severe Dengue;

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