STUDY OF DENGUE INFECTION IN RURAL RAJASTHANManisha Rathi¹, Rupesh Masand², Alok Purohit³**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Dengue has a wide spectrum of clinical presentation in paediatric population, often with unpredictable evolution and outcome. **AIMS:** To record the clinical, laboratory & radiological profile of dengue in hospitalized children and to enlist the predictive markers of severity in patients with severe dengue. **SETTINGS AND DESIGN:** This observational, prospective hospital-based study was conducted in 100 admitted children aged 9 months - 18 years with clinical and laboratory confirmation of dengue illness. **METHODS:** All the 100 subjects included in this study were classified in three groups- Dengue without warning signs (D) Dengue with warning signs (DW) and severe dengue (SD) on the basis of 2009 WHO Guidelines followed by laboratory and radiological evaluation. **STATISTICAL ANALYSIS:** involved summarizing the continuous variables as mean and standard deviation, while nominal/categorical variables were expressed as percentages. Chi square test was used for analysis of nominal/categorical variables. Stepwise Multivariate Logistic Regression analysis was employed to determine the predictors for severe dengue. **RESULTS:** 52 patients had dengue without warning signs (D), 40 patients had dengue with warning signs (DW) and 8 patients had severe dengue (SD). Fever was present in 52(100%) cases, myalgia in 31(59.62%) cases followed by hepatomegaly in 20(38.46%) cases was seen in D group while in DW group fever in 40(100%), vomiting in 34(85%), pain abdomen in 33(82.50%) and hepatomegaly in 11(52.50%) cases was seen. In SD group, fever, myalgia, vomiting, pain abdomen, rash, positive Hess test, pallor, hepatomegaly was observed in all the cases (P value <0.001). Presence of commonly described features like rash (13%), positive Hess test (8%) and bleeding manifestations (7%) in few cases only was a prominent feature observed in the study subjects. Raised SGOT/ SGPT levels, prolonged PT and APTT, hypoalbuminemia, pleural effusion in skiagrams of chest and increased gall bladder wall thickness (GBWT)>3mm in USG scan was significantly associated with SD. Among several predictors, GBWT was observed to be strongly correlating with severity of dengue infection. **CONCLUSION:** Dengue is becoming more prevalent in India especially in rural areas. As it may have a non-specific presentation, it should be suspected in every case of febrile illness in post-monsoon season.

KEYWORDS: Dengue; rural; children.

INTRODUCTION: Dengue is an acute febrile disease caused by the mosquito-borne dengue virus (DENV) of the Flaviviridae family.¹ The World Health Organization (WHO) approximates an annual incidence of 100 million infections out of which 500,000 people with dengue hemorrhagic fever (DHF) require hospitalization, with a large proportion being children. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and in the present decade, from urban to rural settings.¹⁻⁴ The infection by either of four DENV serotypes- 1 to 4 may be asymptomatic or may present as undifferentiated acute febrile illness, classical dengue fever (DF) or as severe dengue- Dengue hemorrhagic fever (DHF) or Dengue shock syndrome (DSS) where the mortality rate is approximately 1-2.5%.⁵ Owing to this variable clinical expression & disease severity

ORIGINAL ARTICLE

and due to the paucity of data regarding its occurrence in paediatric population of adjoining rural areas, this study was conducted to record the clinical, laboratory and the radiological profile of dengue illness in hospitalized children belonging from rural areas of Jaipur district in Rajasthan & to enlist the predictive markers of severity in patients with severe dengue.

METHODS AND MATERIALS: This observational, prospective, hospital-based study was conducted in the Department of Paediatrics, NIMS Medical College and Hospital, Jaipur between January 2013 and December 2013 after obtaining clearance from Institutional Ethical Committee and informed consent from the parent/ guardian of study subjects. This tertiary care Centre is located 50 km from Jaipur City amidst rural surroundings. 100 children between the age group of 2 months to 18 yrs admitted in the Paediatric Ward or Paediatric intensive care unit with symptoms and signs suggestive of dengue illness and with serological confirmation (NS1, IgM and/or IgG positive for dengue with rapid diagnostic kit) were included in the study. Patients with NS1-negative or IgM and IgG-negative dengue- like illness, or bearing concomitant presence of other infections such as malaria, typhoid, hepatitis A and scrub typhus were excluded from this study. After taking a detailed history and performing a meticulous clinical examination, laboratory investigations were carried out which included hemoglobin, total and differential white blood cell (WBC) count, platelet count, hematocrit (Hct), peripheral blood smear, rapid diagnostic tests for Malaria parasite, typhoid and scrub typhus, IgM for Hepatitis A virus, prothrombin time (PT), partial thromboplastin time (PTT), liver function tests, renal function tests, radiological investigations like chest X-ray, ultrasonography (USG) of abdomen and chest and as warranted by the clinical condition of the study subjects.

Tourniquet test was performed by inflating the appropriately sized blood pressure (BP) cuff on the upper arm to a point midway between systolic BP and diastolic BP for 5 minutes. If the resulting petechiae in an area of 6.25cm² (i.e. 2.5 x 2.5cm) was ≥ 20 , it was considered a positive test. Heart rate, BP, platelet count & haematocrit were monitored daily for first five days after admission. The study subjects were classified and grouped on the basis of their clinical presentation, according to the new WHO/ TDR classification 2009⁶ as Dengue without warning sign (D), Dengue with warning signs (DW) and Severe Dengue (SD) following which treatment was commenced as per standard WHO 2011 Guidelines.⁷ The clinical, laboratory and radiological investigations of all the study subjects was recorded in a specially designed pretested proforma. Qualitative detection of NS1, IgM and IgG was performed by using rapid diagnostic test kit (Dengue Day1 TestTM manufactured by J. Mitra and Co. Pvt Ltd) on human serum or plasma sample.

Statistical analysis involved summarizing the continuous variables as mean and standard deviation, while nominal/categorical variables were expressed as percentages. Chi square test was used for analysis of nominal/categorical variables. Stepwise Multivariate Logistic Regression analysis was done to find out predictors for severe dengue. All the analysis as mentioned above was performed using Med Calc 14.0.0 version software. P value <0.05 was taken as significant.

ETHICS: The permission to carry out the study was granted by NIMS Ethics Committee.

RESULTS: A total of 100 patients were included in this study. 51(51%) patients were >12 yrs of age followed by 23(23%) in age group of 8-12 yrs (Table 1). The mean age was 11.60 years. The youngest in the series was 9 months and oldest was 18 yrs of age. M: F ratio was 2.6:1.

ORIGINAL ARTICLE

52(52%) cases were classified in group of Dengue without warning signs (D) followed by 40 (40%) cases in group of Dengue with warning signs (DW) and 8(8%) cases in severe dengue (SD) group. (Fig. 1)

During the study period from January till December 2013, majority of the study subjects were admitted in the months of August (17%), September (43%) and October (26%), (Fig. 2). Fever was reported in 52(100%) cases followed by myalgia in 31(59.62%) and hepatomegaly in 20(38.46%) cases in D group while in DW group, fever was observed in 40(100%) followed by vomiting in 34(85%), pain abdomen in 33(82.50%) and hepatomegaly in 11(52.50%) cases. In SD group presence of fever, myalgia, vomiting, pain in abdomen, rash, positive Hess test, pallor, hepatomegaly was seen in all the cases (P value <0.001.). Presence of commonly described features like rash (13%), positive Hess test (8%) and bleeding manifestations (7%) in only few cases was a prominent feature observed in the study subjects. (Table 2)

Laboratory, serological and radiological analysis have been summarized in Table 3, 4, 5 & 6. In this study, leucopenia was seen in 43(43%) cases and particularly had no relation with severity of dengue illness (P=0.167). Thrombocytopenia was characteristically observed in 75(75%) cases. However, a normal platelet count was conspicuously recorded in the remaining (25%) subjects. Bleeding manifestations were observed in 7 cases only. In 1 case of SD group, it was significantly absent even with a platelet count of $< 20 \times 10^9/L$. Raised SGOT and SGPT levels, prolonged PT and APTT, hypoalbuminemia, pleural effusion in skiagrams of chest and increased gall bladder wall thickness (GBWT) > 3mm in USG scan was significantly ($p < 0.05$) associated with SD. NS1 positivity was significantly helpful in early diagnosis of dengue illness as compared with patients presenting with SD where qualitative IgM and IgG estimation established the diagnosis. In the Stepwise Multivariate Logistic Regression analysis model, the features entered as independent factors were prolonged PT, APTT, hypoalbuminemia ($< 2.5g/dl$), positive Hess test, Positive IgM and increased GBWT > 3 mm. Only GBWT was retained in model as significant predictive marker for severe dengue (OR=66; 95%CI 9.9892 to 436.0721). 94% of cases were correctly classified by model (AUC of ROC curve=0.853).

DISCUSSION: This study was performed to document the clinical, laboratory and radiological profile of dengue fever in children belonging from rural areas of Jaipur district in Rajasthan. Though the study was carried out between January and December 2013, majority of cases were admitted during the monsoon and post monsoon period i.e. September and October which is similar to the observation by Kulkarni et al⁸ and Rasul et al.⁹

Out of a total of 100 dengue sero-positive cases, 52(52%) patients had D, 40(40%) patients had DW and 8(8%) patients had SD. Though 52% of study subjects presented without warning signs, they were still admitted in the Paediatric Ward owing to apprehension among parents in relation to the disease manifestations and occurrence of similar such cases in their neighbourhood.

In this study, age of the study subjects ranged from 9 month-18 years (mean =11.6 years). Shah et al¹⁰ observed a similar age range of 8 month - 14 years in their study. Other studies¹¹⁻¹² have observed a mean age of 8.3 years and 4.9 years respectively. Neonatal Dengue is very rare. None of the subjects were neonates in this study. However, there were two affected infants aged 9 months each. Kulkarni et al⁸ observed 6 neonates affected with dengue fever. This may be partly explained by the larger sample size (n = 948) considered in their study.

ORIGINAL ARTICLE

In the present study, more than two-thirds of the study subjects were males. This observation may be explained by the fact that all our study subjects belonged from rural areas where gender bias is highly prevalent and was similar to that observed by Kulkarni et al.⁸ A higher proportion (60%) of severe dengue in female children than in males was observed which is in consonance with Kabra et al.¹³ Fever was observed in all the study subjects with a mean ($\pm$ SD) duration of 5.42($\pm$ 3.69) days, which was similar to other studies.¹⁴⁻¹⁶ None of the patients had classic biphasic fever and 'break-bone' fever, as classically described in dengue and as similarly observed by Joshi et al.¹⁴ Altered sensorium with absence of seizures was present in four patients of SD group. This may be explained by the fact that dengue infection can cause neurologic manifestations secondary to cerebral hypoperfusion as in shock. However, encephalopathy as a complication was observed in one patient of severe dengue among the above. Unusual or atypical presentations like an upper respiratory tract infection, diarrhea, jaundice, exfoliative dermatitis were not observed, as recorded by Ratageri et al.¹⁵ in their study.

Out of 100 cases, bleeding manifestations were observed in 7 cases only in the form of petechiae (n= 2), epistaxis (n=2), melena (n= 1) and haemetemesis (n= 1). This is in contrast to the observation by other authors^{11,14-16} who observed significant number of cases with bleeding manifestations.

Hess (Tourniquet) test was positive in only eight patients (8%) of study subjects, in contrast to other studies^{8,10} where it was positive in a significantly higher percentage of patients. Low proportion of positive tourniquet test in our patients may be due to the darker skin color or due to the different strain of dengue virus affecting the Indian subcontinent.¹⁶ This test has a sensitivity of 41.6%, specificity of 94.4%, positive predictive value of 98.3%, and negative predictive value of 17.3% for dengue infection.¹⁷

A possible reason for the significant differences seen in the clinical expression of the disease mentioned in different studies (Table 7) may be due to infection with different DENV serotypes and the possibility of concurrent infections with more than one serotype. Co-circulation of multiple DENV serotypes has been reported from many parts of the world, including India during an outbreak of DHF/DSS in 2006. There is, however, limited documentation describing concurrent infections with more than one serotype in the same individual.^{18,19} Furthermore, as already alluded to, sequential infection with more than one serotype is thought to be a major factor for the emergence of DHF. However, virulence is not the only factor to explain differences in host susceptibility to the disease and disease severity. Host immune response variations have been associated with polymorphism in the human genome, which may help explain why some patients develop end-stage complications in dengue disease and others only experience a mild form of the disease. In another study of children with DENV infection, host genetic differences were shown to affect the immune response and consequently, influence disease outcome.^{20,21}

There was no significant statistical correlation between hematocrit and severity of disease among the clinical subgroups of dengue. The classical description of >20% rise in the hematocrit is difficult to establish, as reference standards have not been established for Indian children. Hence the rise in hematocrit was not taken as a diagnostic criteria. Moreover, Indian children with SD have a lower than expected rise in hematocrit during the plasma leakage period. This has been attributed to the high prevalence of iron deficiency anemia in the general population. Thus, hematocrit may not be a good indicator of monitoring fluid therapy in infants and children in presence of moderate anemia

ORIGINAL ARTICLE

in our study population. However, the criterion of >20% fall in hematocrit level after sufficient treatment with intravenous fluid therapy may help in retrospective diagnosis of DW and SD groups. Further research is required in this direction to establish age related baseline hematocrit values in Indian children. There was no correlation between low platelets count (75% cases) and bleeding manifestations (n=7) in this study. However, bleeding was observed in cases with severe thrombocytopenia (statistically significant) associated with severe dengue in 6 out of 8 cases. This is in contrast to studies by Joshi et al¹⁴ (96%) and Dhooria et al²² who observed thrombocytopenia in all their study subjects.

The platelet counts on hospital admission were neither an indicator of prognosis nor of progression of the disease. 25 patients in this study had a normal platelet count on admission despite having serological evidence of dengue infection. However, studies which include only severe dengue cases show correlation between low platelet count and bleeding manifestations as observed by other authors.^{16,23} However, platelet count provides a very useful means of diagnosis at the screening level.

Both SGOT and SGPT were observed to be raised in 80% of study subjects. Elevation of SGOT was more compared with SGPT in the present study and was similar to other observations. It may be due to involvement of myocytes which has clinically manifested as myalgia. The present study did not demonstrate a significant difference in the LFT's between the clinical subgroups of dengue. Though, raised transaminase level may be deemed as non-specific marker of infection and stress but in combination with vomiting and hepatomegaly may serve as an indicator of dengue infection during an epidemic.

Ultrasound was found to be superior when compared with chest x-ray to detect plasma leakage. The low sensitivity of radiograph is because of the fact that x-ray films are not ideal for detecting small amounts of effusion while ultrasound is highly helpful. An earlier study from Indonesia also reported such discrepancies in findings related to these investigations. Ultrasound is ideal owing to its safety and that it is non-ionizing and would assist in detecting plasma leakage even before it clinically manifests. Similar findings have been reported earlier from Indonesia.²⁴

NS1 Ag circulates uniformly in all serotypes of dengue virus and it circulates at high level during the first few days of illness.²⁵ NS1 Ag levels varies from 0.04 - 2 µg/ml in acute-phase serum samples, to only 0.04µg/ml or even less in convalescent phase serum.²⁶ This is the reason for its higher detection rate in acute phase sera. In this study, patients with D (78%) and DW (67.5%) were diagnosed using NS1 antigen detection test kit. However patients with severe dengue were negative for NS1 antigen owing to fact that they had febrile illness of more than eight days duration.

The morbidity and the mortality of dengue illness can be reduced by early diagnosis, hospitalization and symptomatic care. In this study 68% study subjects were detected in the first four days of illness by NS1 Ag assay. Studies claim that in addition to an early diagnosis, NS1 antigen may be an indicator of disease severity.²⁶ Libraty et al observed that a very high concentration of NS1 antigen within 72 hours of illness identified patients at risk of developing DHF.²⁷ A quantitative estimation of NS1 Ag was however, not carried out in this study to confirm this observation.

Detection of specific IgM by MAC-ELISA is still used as the diagnostic technique for acute infection; its disadvantage being delayed appearance of antibodies from 5-10 days after the onset of illness in case of primary dengue virus infection and 4-5 days after the onset of illness in secondary infections.²⁸ The requirement of paired sera, subsequently in convalescent phase, if negative in acute phase also delays diagnosis. Sensitivity and specificity of IgM and IgG detection by test kit is 100%

ORIGINAL ARTICLE

and 99.98% respectively and for NS1, sensitivity and specificity is 100% and 99.94%. Serological investigation for IgM detection in convalescent period could not be performed in this study owing to financial limitations.

In this study all 100 patients were given intravenous fluid and antipyretics. Platelet transfusion was given in 3 cases of severe dengue. It was observed that outcome of patients does not correlate with platelet transfusion and it was statistically significant (p value <0.05). Moreover, mortality was observed in those three cases despite platelet transfusion.

Out of 100 children, 97 cases recovered without any sequelae and were discharged subsequently. Mortality was observed in 3(3%) cases due to acute respiratory distress syndrome ($n=2$) and encephalopathy ($n=1$). All three patients were admitted in PICU and required mechanical ventilation.

Gall bladder wall thickness (GBWT) >3 mm in USG scan was observed as significant predictive marker for severe dengue (OR =66; 95% CI 9.9892 to 436.0721) in this study which was similar to the observation by other authors.^{8,29,30}

The limitations of this study were that some cases exhibiting symptoms and signs suggestive of dengue illness were not included because they were sero-negative for dengue infection. Specific serotype detection facility for dengue virus was not available at institutional level. Further, advanced techniques like ELISA were unavailable, hence could not be employed to detect IgM and IgG for dengue infections.

To conclude, dengue illness may have a non-specific and varied presentation in pediatric population, thus mandating its screening in every case of febrile illness especially during the post-monsoon season of the year. NS1 antigen detection test facilitates early diagnosis and GBWT predicts severity of severe dengue effectively.

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ORIGINAL ARTICLE

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ORIGINAL ARTICLE

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Age Grp (in years)	n	Dengue Classification					
		Without Warning Signs (n=52)		With Warning Signs (n=40)		Severe (n=8)	
		No.	%	No.	%	No.	%
<1	2	2	3.85	0	0.00	0	0.00
1-4	3	3	5.77	0	0.00	0	0.00
>4-8	21	11	21.15	10	25.00	0	0.00
>8-12	23	8	15.38	12	30.00	3	37.50
>12	51	28	53.85	18	45.00	5	62.50
Total	100	52	100.00	40	100.00	8	100.00

Table 1: Age distribution of study subjects

ORIGINAL ARTICLE

Symptoms/Signs	N	Dengue Classification						'p' Value
		Without warning signs (n=52)		With warning signs (n=40)		Severe (n=8)		
		No.	%	No.	%	No.	%	
Fever	100	52	100.00	40	100.00	8	100.00	NA
Vomiting	42	0	0.00	34	85.00	8	100.00	<0.001
Pain Abdomen	42	1	1.92	33	82.50	8	100.00	<0.001
Myalgia	69	31	59.62	30	75.00	8	100.00	0.041
Rash	13	0	0.00	5	12.50	8	100.00	<0.001
Bleeding Manifest'n	7	0	0	1	2.50	6	75.00	<0.001
Positive Hess Test	8	0	0.00	0	0.00	8	100.00	<0.001
Respiratory Distress	5	0	0.00	0	0.00	5	62.50	<0.001
Altered Sensorium	4	0	0.00	0	0.00	4	50.00	<0.001
Pallor	21	7	13.46	6	15.00	8	100.00	<0.001
Lymphadenopathy	7	2	3.85	1	2.50	4	50.00	<0.001
Flushing	7	2	3.85	1	2.50	4	50.00	<0.001
Cold Extremities	7	1	1.92	0	0.00	6	75.00	<0.001
Hepatomegaly	39	20	38.46	11	52.50	8	100	0.004

Table 2: Analysis of Symptoms and Signs

Investigation	Mean(Range)
Hemoglobin	10.75(6.30 -14.20) g/dl
Hematocrit	33.91%(17.40-43.70)
Total leukocyte count	4.9×10 ⁹ (1.7×10 ⁹ -17×10 ⁹)/L
Platelet count	82×10 ⁹ (15×10 ⁹ -274×10 ⁹)/L
Prothrombin time	13.93(11-30) sec*
Activated partial thromboplastin time	31.50(26-46) sec*
SGOT	165.26(26-900) U/L
SGPT	124.22(24-765) U/L
Serum albumin	3.90(2.20-4.60) g/dl
*Sec-seconds	

Table 3: Laboratory investigations in study subjects

Test Result		Dengue Classification						'p' Value
	N	Without warning signs (n=52)		With warning signs (n=40)		Severe (n=8)		
		No.	%	No.	%	No.	%	
NS1 Positive	68	41	78.85	27	67.50	0	0.00	<0.001
IgM Positive	35	12	23.08	18	45.00	5	62.50	0.012
IgG Positive	26	8	15.38	10	25.00	8	100.00	<0.001

Table 4: Serological analysis of the study subjects

ORIGINAL ARTICLE

Chest X-ray	No. of cases	%age	Dengue Classification		
			Without Warning Signs (n=52)	With Warning Signs (n=40)	Severe (n=8)
Normal	80	80	49	29	2
Pleural effusion left side	1	1	0	0	1
Pleural effusion right side	15	15	3	10	2
Pleural effusion bilateral	4	4	0	1	3
Total	100	100	52	40	8

Table 5: Chest X-Ray findings in study subjects

USG	No. of cases	Percentage (%)	Dengue Classification			P value
			Without Warning Signs (n=52)	With Warning Signs (n=40)	Severe (n=8)	
Ascites	4	4	2	2	0	<0.001
Pleural Effusion(PE)	9	9	0	2	7	
Ascites + PE	8	8	1	6	1	
Ascites + PE+GBWT	3	3	0	0	3	
Hepatosplenomegaly(HS)	7	7	0	7	0	
Ascites + HS	1	1	0	0	1	
Hepatomegaly(H)	4	4	2	2	0	
H + PE	1	1	0	1	0	

Table 6: Findings of ultrasonography (USG) scan in study subjects

* Altered sensorium.

Clinical features (in %age)	Agarwal et al ³¹	Joshi et al ¹⁵	Richard et al ³²	Ratageri et al ¹⁷	Mittal et al ¹¹	Batra et al ³³	Mandal et al ³⁴	Shah et al ¹²	Narayanan et al ²⁰	Present Study
Fever	100	100	100	100	100	100	100	100	98.3	100
Headache	-	15.8	96.70	22	63	-	62.16	-	28.8	-
Rash	-	-	26	24	-	24	37.84	41	8.5	13
Myalgia	-	7	39.1	-	-	8	-	-	-	69
Pain Abdomen	49	31.5	39.1	52	71	52	-	-	23.7	42
Vomiting	68	40.3	47.8	72	-	72	-	86.60	83	42
Alt.sens* /seizures	8	12.3	17.4	20	-	-	11.11	48.70	-	4
Petechiae	-	-	43.5	-	-	-	-	-	-	3
Hemetemesis	-	31.8	-	18	35.5	-	-	-	66.1	1
Melena	-	27.2	-	-	-	-	-	-	-	1
Epistaxis	-	63.6	-	-	-	-	-	-	-	2
Lymphadenopathy	-	18.2	-	4	-	-	-	-	10.2	7
Shock	8.2	31.6	11.1	8	42	-	-	35.3	22	7
Hepatomegaly	72	66.6	-	-	31.1	56	-	-	52.5	39

Table 7: Comparative analysis of prominent clinical features in present study with other Indian studies^{11,12,15,17,20,31,33,34} and a Indonesian study³²

Fig. 1: Categorization of study subjects according to the new WHO / TDR Classification 2009

Fig 2: Month-wise distribution of study subjects

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