

A Prospective Study of Predictors and Outcome of Severe Dengue Illness in Children

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Abstract

Introduction: Dengue fever causes a high burden of disease and mortality across tropical and subtropical regions in Southeast Asia, Africa, the Western Pacific, and the Americas. Dengue virus comprises five serotypes, DENV-1, DENV-2, DENV-3, DENV-4 and DENV-5, which are transmitted by *Aedes aegypti* mosquitoes. An estimated 2.5 billion people worldwide are at risk of dengue. More than 50 million dengue infections are estimated to occur annually, of which approximately 500,000 result in hospital admissions for severe dengue in the form of dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), principally among children.

Materials and Methods: This is a hospital based prospective study done at the Department of Paediatrics, GVR Children Hospital, Kurnool during the Monsoon season in 2019. Children diagnosed to have Dengue fever and confirmed by NS1 Ag test or IgM Elisa were included. Children were classified into 3 clinical groups and compared. Comparison was also made in 2 groups as dengue with warning signs and severe dengue as per WHO 2015 clinical guidelines, to find out the predictors of severity. Qualitative data was analysed and expressed in proportions and quantitative data in mean and standard deviation. Chi-square (χ^2) test was used to evaluate the association between qualitative variables and ANOVA for quantitative variables. *p* value less than 0.05 was considered significant. SPSS 16.0 software was used for statistical analysis.

Results: A total of 235 children were included of which 132(56.2%) were boys and 103 (43.8%) were females. (M: F=1.28:1). The highest number of admissions were from kurnool, 164 - (69.7%) followed by dhone 63- (26.8%) and nandhyal 8-(3.5%). Admissions were maximum in the month of June (68) followed by July (57) and August (53). 0-1 age group included 19 infants. (8.1%) and 39 (16.5%) were more than 10 years of age. Mean age of the series was 6.61 (SD 3.49) years and 19 (8.2%) were infants. Mild Protein energy malnutrition in 41 children, grade 2 PEM in 5 cases and grade 4 PEM in two children.

Conclusion: Dengue fever can affect children irrespective of their age or nutritional status. Older children and male sex were found to be more affected. There are definite clinical and lab parameters which can predict the severity in Dengue fever. Though severe illness is associated with high morbidity early diagnosis and timely appropriate clinical management, correction of dehydration along with proper referral system can save the children. The mortality can be reduced to zero even in patients having expanded dengue syndrome and Dengue shock syndrome. None of the comorbidities had affected the outcome.

Key Words: Dengue fever, PEM, DHF, DSS.

Date of Submission: 26-05-2020

Date of Acceptance: 13-06-2020

I. Introduction

Dengue fever causes a high burden of disease and mortality across tropical and subtropical regions in Southeast Asia, Africa, the Western Pacific, and the Americas. Dengue virus comprises five serotypes, DENV-1, DENV-2, DENV-3, DENV-4 and DENV-5, which are transmitted by *Aedes aegypti* mosquitoes. An estimated 2.5 billion people worldwide are at risk of dengue. More than 50 million dengue infections are estimated to occur annually, of which approximately 500,000 result in hospital admissions for severe dengue in the form of dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), principally among children.

Dengue infection is frequently confounded with other febrile illnesses (OFI), presenting with non-specific clinical symptoms and clinical features analogous to OFI. During the early stages of dengue, the presence of non-specific febrile illness makes precise diagnosis strikingly difficult, resulting in inefficient treatment and possible increases in morbidity and mortality. Severe dengue fever, if not appropriately managed, may lead to rapid death, particularly in children. In addition, the lack of necessary laboratory facilities, particularly in remote, rural areas, may cause difficulty in discriminating dengue infection from OFI. Dengue is

one of the most common vector-borne diseases in Southeast Asia, and one of the most important mosquito-borne viral diseases with an epidemic potential in the world.

We wanted to study the clinical and epidemiological profile of dengue fever in children. We also wanted to study the predictors and outcome of severe dengue illness by comparing the clinical and lab parameters in children having dengue with warning signs and severe dengue.

II. Materials And Methods

This is a prospective study conducted in the Department of Paediatrics, GVR Children Hospital, Kurnool from March 2019 to September 2019 (monsoon season in Andhra Pradesh).

Sample Size Calculation

Sample size was calculated using the formula

$$N=(Z\alpha+Z\beta)22 SD2/d2$$

where, $Z\alpha= 2.576$, a constant for $\alpha=1\%$ $Z\beta=1.64$, a constant for $\beta=5\%$, Power of the study= $1-\beta= 95\%$,

$$SD=(SD1 + SD2)/2d= \mu1-\mu2= \text{difference between means}$$

As per the reference study 'Clinical profile and outcome of children admitted with dengue fever in a tertiary care hospital in South India'. by Kumar BV, Simna L, Kalpana D, Kailas L. (From departments of Paediatrics, GVR Children Hospital, Kurnool)

$$SD1= 115SD2= 27\mu1= 92\mu2= 98 \text{ (from SGPT values of the reference study)}$$

$$N=(Z\alpha+Z\beta)22 SD2/d2 =218$$

Inclusion Criteria

Children admitted to Paediatric ward or ICU diagnosed as Dengue fever with clinical features and laboratory parameters were selected. Those confirmed on consecutive sampling by NS1Ag test or IgM Elisa were included.

Exclusion Criteria

Those children with other chronic illnesses diagnosed to have Dengue fever.

Results of laboratory parameters like complete blood count, including packed cell volume, platelet count, LFT,RFT,RBS, Serum calcium and Electrolytes, were collected. Coagulation profile, serum IgG, ultrasound abdomen, MRI, and chest radiography were performed only if clinically indicated. Children were classified according to WHO guidelines 2015.

Atypical features and complications with immediate outcome measures were noted.(5) Patients were followed up daily to assess clinical and laboratory progression till discharge and subsequently in outpatient care if required. Children with chronic co morbidities were also observed and analysed separately to know the outcome.

Statistical Analysis

The statistical analysis was done using SPSS. Qualitative data was analysed and expressed in proportions and quantitative data in mean and standard deviation. The discrete variables were analysed using Chi-Square test, and continuous variables using ANOVA. The analysis was performed using SPSS 16.0 software. p value less than 0.05 was considered as significant.

III. Results

A total of 235 children were included of which 132(56.2%) were boys and 103 (43.8%) were females. (M: F=1.28:1).The highest number of admissions were from kurnool, 164 - (69.7%) followed by dhone 63-(26.8%) and nandhyal 8-(3.5%). Admissions were maximum in the month of June (68) followed by July (57) and August (53). 0-1 age group included 19 infants. (8.1%) and 39 (16.5%) were more than 10 years of age. Mean age of the series was 6.61 (SD 3.49) years and 19 (8.2%) were infants. Mild Protein energy malnutrition in 41 children, grade 2 PEM in 5 cases and grade 4 PEM in two children.

Clinical classification among the study group showed 77 (32.9%) had mild dengue fever, 106 (45.29%) had dengue with warning signs and 52 (22.22%) had severe dengue fever. Dengue shock syndrome was present in 17 children. Children were initially compared in 3 groups as mild dengue, Dengue with warning signs, and severe dengue. Comparison was also made in 2 groups as mild 167-(71.4%) and severe dengue (67-28.6%) as per WHO 2015 clinical guidelines to know the predictors of progression to severe dengue. Multiple variables were also compared in dengue with warning signs and severe dengue.

Clinical manifestations included Rash (40.7%) myalgia (53.3%), arthralgia (26.4%), vomiting (62.2%), diarrhoea (12.5%), abdominal pain (63.8%), headache (37.7%), generalised lymphadenopathy (23.8%), oedema (28.8%), lethargy (48.1%) flushing (47.5%) bleeding manifestations (32.2%). Hess test was positive in 25.21% Mucosal bleeds were manifested in (25.7%) children. Bradycardia (10.5%) Hypotension (21.9%) & manifestations in the eyes (39.8%). Laboratory investigations revealed anaemia (17.9%), thrombocytopenia (83.8%), Leucopenia (59.9%), Relative lymphocytosis (67.6%) leucocytosis (6.1%), elevated hepatic enzymes (55.7%), Abnormal RFT (4.1%), hyponatremia (26.5%) hypoalbuminemia (24.7%) Dengue NS1 antigen was positive in (91.6%) and IgM dengue positivity was shown in (85.7%).

Fever was present in almost all children with an average duration of 4.8 days. p value was found to be significant for vomiting, diarrhoea, abdominal pain, bleeding manifestations including mucosal bleed, positive Hess test, excessive tiredness, hypotension flushing and eye changes when mild and severe dengue were compared. Among the lab parameters. p value were found to be significant for platelet count, liver function tests, renal function tests, serum sodium, serum albumin and radiological changes. Leucopenia, relative lymphocytosis and elevated PCV were not found to be significant.

The changes in the eye observed were periorbital puffiness, sub conjunctival haemorrhage, Retro orbital pain, and macular haemorrhage. Independent predictors were found to be abdominal pain or tenderness, persistent vomiting, lethargy, mucosal bleed, clinical fluid accumulation, hepatomegaly >2 cm, platelet count <100 × 10⁹/L. Outcome measure of severe dengue were defined as per WHO guidelines 2015. Mean duration of hospital stay 4.17 +(2.613) days.

Radiological evaluation of these children revealed Pleural effusion in 33 cases, 16 had bilateral & unilateral effusion in 17 cases with predominant right sided involvement. 28 children had ascites. Perinephric collection and severe hemoperitoneum were seen in 3 children. 2 children had pericardial effusion. The radiological findings seen in gall bladder included cholecystitis, Cholangitis Peri gall bladder collection Gall bladder wall oedema and sludge in bladder. PT and APTT values were deranged in 42 cases among the severely affected group. Isolated PT prolongation was seen in 9 cases (17.3 %), APTT prolongation in 19 (38%) while both were deranged in 12 (23 %) of dengue shock syndrome. AST (SGOT) values > 100 units in 36 cases of severe dengue with values observed more than 3000 in 3 cases.

S.No	Age	No of Patients	Percentage
1	0-1 year	19	8.05
2	1-5 years	79	33.6%
3	5-10 years	98	41.7%
4	>10 years	39	16.59%

Table 1: Age Wise Distribution

Parameter	Variable	DWS	DSS	P Value
Platelet Count	<50000 /cu.mm	23	27	0.001
	50000-1 lakh	53	19	
	1-1.5 lakhs	19	5	
	>1.5 lakh	11	1	
Serum Sodium	<130 meq/l	15	20	0.001
	130-135	19	11	
	>135	21	10	
SGOT	<200 units	76	35	0.005
	>200	6	12	
Serum Albumin	<2.5 gm/dl	16	29	0.001
	2.5-3	59	19	
RBS	40-70 mg/dl	64	104	0.001
	>70 mg/dl	41	25	

Table 2: Multiple Comparison of Lab Parameters in DWS and Severe Dengue

Lab Parameter	Mild	DWS	Severe Dengue
Hb	12.13±1.186	11.99±1.80	11.97±1.96
PCV	34.67±7.72	36.57±4.13	35.96±7.49
Platelet Count	52430±6055	90613.21±50028.67	58653.85±36686.2
SGOT	153.55±151.93	213±429.57	469.39±794.5
SGPT	77.84±69.49	99.32±162.87	165.49±281.34
Serum Sodium	134±3.4	133.95±8.157	129.88±5.853
Serum Albumin	2.283±0.147	3.055±0.458	2.194±0.55

Table 3: The Mean Values of Lab Parameters in Mild, DWS (Dengue with Warning Signs) & Severe Dengue

Parameter	F Value	Significance
Hb	.540	.583
PCV	1.826	.164
Platelet	21.56	.000
SGOT	6.249	.002
SGPT	3.125	.049
Serum Sodium	7.029	.001
Serum Albumin	23.167	.000

Table 4: Comparison of The 3 Clinical Groups Using ANOVA

Dependent Variable	Type	Significance
Platelet Count	1 2	.001
	1 3	.000
	2 3	.000
Serum Sodium	1 2	.170
	1 3	.001
	2 3	.068
Serum Albumin	1 2	.094
	1 3	.000
	2 3	.000
SGOT	1 2	1.00
	1 3	.003
	2 3	.010

Table 5: Post HOC Analysis of Dengue Illness in 3 Groups as Type 1 Mild, Type 2 DWS, & Type 3 Severe

System Involved	Unusual Atypical Manifestations	Number
Neuromuscular	Encephalopathy	4
	Transient weakness	2
	Myositis with high CPK	2
	Febrile seizures	6
	ADEM	1
Cardiovascular	Arrhythmias- transient 2:1 block	1
	Bradycardia with ectopics	2
	Myocarditis	2
	Pericardial Effusion	1
Respiratory	Severe LRTI – ventilator support	9
	ARDS	4
	Pleural effusion	33
	Collapse lung	3
Gastrointestinal	Hepatic involvement	41
	Fulminant hepatic failure	4
	cholecystitis	8
	Clinical jaundice	3
Hematological	Coagulopathy	42
	HLH	3
Eyes	Subconjunctival bleed	4
	Macular haemorrhage with partial visual loss	1
Renal	AKI	4
	HUS	2
	MODS	4

Table 6: Expanded Dengue Syndrome

IV. Discussion

Compared to previous years, there was a significant rise in number of admissions during 2017 followed by a decline in the incidence thereafter. Maximum admissions were during the month of July and August. Most of the cases were referred from Kurnool, Nandhyal and Dhone areas. In the present study it was found that males were more affected with a male to female ratio of 1.28:1 as reported in most of the studies A few studies have reported more incidence in females.

Mean age of the group was 6.61 ± 3.497 years. Infants constituted 8.2 % and 57.7% of children belonged to 5-15 age group in our study group similar to that seen in study conducted by Manjunadh et al. Study by Mittal et al showed 68% cases were in the age group of 6-12 years, only 2.9% were infants and the mean age group was 8.3 ± 3.5 years. A study conducted by Misra S et al in 2016 also shows similar results. Among the group 4 infants belonged to less than 6 months of age but the age group showed no association with severity of illness when the different age groups were compared.

Only 22.4% children had protein energy malnutrition and most of the children had normal weight. It has been reported that children having better nutritional status can also have more complications due to better immunological response.

Among the study group, 77 had mild dengue fever, 106 had dengue with warning signs and 52 had severe dengue fever as per the latest WHO classification. There was an overlapping of clinical signs among Dengue with warning signs, severe Dengue, including expanded dengue syndrome and severe dengue shock syndrome (DSS) as described in WHO national guidelines.

Fever was present in almost all the cases (94.8%) and the mean duration was 4.8 days similar as described in most of the studies. Vomiting and abdominal pain, myalgia, lethargy, rash, Flushing, bleeding manifestations were the most common symptoms at presentation.

Generalized lymph node enlargement was seen in (23.8%) with features of lymph node abscess in 3 children. A study from Trivandrum shows less incidence of lymphadenopathy. Hepatomegaly alone was seen in 73 children, 46 had hepatosplenomegaly with enlarged tender liver in 14 cases and 8 had splenomegaly alone. These findings were significantly associated with severe dengue with a p value of 0.002, similar to the results described by Mohan et al. Clinical jaundice was present only in 3 children similar to that reported in the study from Trivandrum. Severe dehydration was present in 12 children and among them 9 had diarrhea. The presentation was with severe pneumonia in 8 children and 4 had features of ARDS.

Leucopenia was seen in 59.9% and Thrombocytopenia in 83.8% which was similar to other prospective observational studies. The mean value of PCV with mild dengue was 35.8 and 36.36 in mild and severe dengue respectively. In our series the elevated values are seen in both severe dengue and dengue with warning signs without any signs of plasma leakage similar to a study by Mohan et al. Many studies have shown significant association of elevated haematocrit. Our study series showed elevated mean hematocrit in both DWS and DSS but the p value was not found to be significant. 5 children had fall in PCV requiring blood transfusion.

V. Conclusion

Dengue fever can affect children irrespective of their age or nutritional status. Older children and male sex were found to be more affected. There are definite clinical and lab parameters which are predictors of the severity of Dengue fever. Though severe illness is associated with high morbidity early diagnosis and timely appropriate clinical management, correction of dehydration along with proper referral system can save the children. The mortality can be reduced to zero even in patients having expanded dengue syndrome and Dengue shock syndrome. None of the comorbidities had affected the outcome.

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Dr.M.Bhuvaneshwari, et. al. "A Prospective Study of Predictors and Outcome of Severe Dengue Illness in Children." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(6), 2020, pp. 01-05.