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Role of early warning signs in children with severe dengue infection

Sriram Pothapregada^{1*}, Vijayalakshmi Sivapurapu², Banupriya Kamalakannan¹, Mahalakshmy Thulasingham³

¹Department of Pediatrics, Indira Gandhi Medical College and Research Institute, Puducherry, India

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*Correspondence:

Dr. Sriram Pothapregada,

E-mail: psriram_ped@yahoo.co.in

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ABSTRACT

Background: The objective of the study was to evaluate and analyze the role of preceding early warning signs at admission in children with severe dengue infection.

Methods: All children (0-12 y of age) diagnosed and confirmed as dengue fever admitted at a tertiary care hospital at Puducherry were retrospectively analysed from hospital case records as per the revised World Health Organization(WHO) guidelines 2009 for dengue fever. The data was analysed by descriptive statistics using SPSS 16.0 statistical software. Early warning signs were analyzed by logistic regression and a P-value of <0.05 was taken as significant.

Results: Out of 360 children confirmed with diagnosis of dengue fever, non-severe and severe dengue infection was seen in 214(59.4%) and 146 cases (40.6%) respectively. The most common manifestation of severe dengue infection were shock (40.6%), bleeding (16.7%) and multiorgan failure (2.2%). On logistic regression, the warning signs most commonly associated with severe dengue infection were pain abdomen, hepatomegaly, hypotension at admission and HCT>20% with concomitant platelet<50,000/mm3. Clinical variables which were unlisted in the revised guidelines but significantly associated with severe dengue infection were Age >6 yrs, retro-orbital pain, palmar erythema, joint pain, splenomegaly, positive tourniquet test, right hypochondriac pain and epigastric tenderness.

Conclusions: Early identification of the preceding warning signs, timely intervention and vigilant monitoring can reduce the morbidity and mortality in children with severe dengue infection. Since there were other clinical variables not enlisted as warning signs but were significantly associated with severe dengue infection, the list of warning signs in the revised guidelines needs to be expanded.

Keywords: Encephalopathy, Severe dengue, Warning signs, World Health Organization

INTRODUCTION

Dengue fever is the most rapidly spreading mosquito borne viral disease worldwide with an estimated 30-fold increase in incidence over last five decades with an unpredictable clinical course and outcome. An estimated 500,000 people with severe dengue infection require hospitalization annually and 90% of them are children<5 years of age. The case fatality rate in severe dengue is more than 20% and with timely intervention, it can be reduced to <1%.

The revised 2009 WHO guidelines have focused on recognized warning signs for early detection and timely

²Department of Critical Care and Anaesthesia, Indira Gandhi Medical College and Research Institute, Puducherry, India

³Department of community medicine, JIPMER, Puducherry, India

intervention and reclassified dengue fever as "Dengue without warning signs" (D), "dengue with warning signs" (DW) and "Severe Dengue" (SD). Atypical manifestations of dengue fever were termed as "Expanded dengue syndrome" which is probably a result of prolonged shock with organ failure, associated comorbidities and co-infections. There is limited literature describing the role of warning signs in children with dengue fever. The primary objective of this study was to evaluate and analyze the role of preceding early warning signs that were predictive of development of severe dengue infection at a tertiary care hospital.

METHODS

After approval by the Institute Ethics committee, case records of all children admitted with dengue fever at a tertiary care hospital at Puducherry from August 2012 to January 2018 were reviewed retrospectively and only confirmed cases of dengue fever were included in the study. The case definition, diagnosis and management were as per the revised World Health Organization (WHO) guidelines 2009 for dengue fever. Dengue fever without warning signs was defined as laboratory confirmed cases with no signs of plasma leakage. Warning signs included persistent vomiting >48 hrs, mucosal bleed, abdominal pain and tenderness, liver enlargement> 2cm, clinical fluid accumulation and increase in HCT with concurrent decrease in platelet count and required strict observation and intervention. Severe dengue included signs of severe plasma leakage, severe organ involvement and severe bleeding.

Details of clinical and laboratory profile, warning signs, and the treatment given were recorded in a predesigned proforma. The diagnosis of dengue fever was confirmed by NS1antigen-based ELISA test (J. Mitra kit, India) or dengue serology for IgM for primary dengue infection and IgG antibodies for secondary dengue infection (Kit from National vector born disease control programmed Pondicherry and National institute of virology Pune, India) during the acute phase and convalescent phase of the illness. Blood samples were collected from children with provisional diagnosis of dengue fever were screened by both NS1 Ag and MAC-ELISA.

Statistical analysis

The SPSS (IL Chicago) 16.0 statistical software and were used for data analysis. After collecting the data, all variables were expressed by descriptive statistics. Continuous data, expressed as mean+SD, or median (range) wherever appropriate. Categorical variables were expressed as frequencies and percentages, and then analyzed by Chi-square or Fisher's exact test, where appropriate.

The degree of association of warning signs with severe dengue infection was determined by univariate analysis. Multivariate analysis and coefficient of binary logistic

regressions were used in children who were statistically significant on univariate analysis. The results were presented as unadjusted odds ratio (OR), adjusted OR, with 95% confidence interval (CI). P<0.05 was taken as significant. The outcome of non-severe dengue infection, and severe dengue infection was determined in terms of mean duration of hospital stay, mean duration of fever at admission, absence of fever and platelet count > 50,000/mm³ at the time of discharge.

RESULTS

Out of 497 children that were admitted with provisional diagnosis of dengue fever the diagnosis was confirmed in 360 cases (72.4%) and only confirmed cases were included in the study. Eleven children were ommited from the study due to incomplete data.

Seven children were referred from primary health centres and the rest of the cases were direct admissions. Non-severe dengue infection and severe dengue infection was seen in 214 (59.4%) and 146 cases (40.6%) respectively. The most common affected age group was 7-12 years (60.5%) and the mean age (SD) of presentation was 7.2(3.4) years. Infants were the least affected sub-group with 13 cases (3.6%). The youngest was a neonate, and the oldest was 12 years of age.

Male to female ratio was 1.1:1. The children that were admitted with dengue fever were from Puducherry (72.7%) and Tamil Nadu (27.3%). The mean duration of hospital stay was 6.5 (2.7) days. The mean (SD) duration of occurrence of severe dengue infection from the onset of warning signs in the febrile phase was 4.9(2.0) days and during the critical phase of illness was 2.6(2.0) days respectively. The mean duration of fever was 4.8 (2.0) days at admission.

The common clinical presentations included fever 340(94.4%), myalgia 275(76.4%), conjunctival congestion 274(76.1%), headache 258(71.7%), coryza 232 (64.4%), palmar erythema 185 (54.1%), retro-orbital pain 153(42.5%), facial flush 100 (27.8%), joint pain 93 (25.8%), and rash in 60 (16.7%) cases. The common atypical manifestations of dengue fever at admission were lymphadenopathy in 105 (29.2%), splenomegaly in 75 (20.8%), biphasic fever in 57 (15.8%), epigastric tenderness in 84 (23.3%), right hypochondriac pain in 55 (15.3%), febrile diarrhea in 33 (9.2%), and seizures in 17 (4.7%) (Table 1).

The most common early warning signs at the time of admission were persistent vomiting 276(76.6%), hepatomegaly 200 (55.5%), cold and clammy extremities 151 (41.9%), pain abdomen 139(38.6%), hypotension 110 (30.5%), restlessness 89 (24.7%), giddiness 79 (21.9%), bleeding 60 (16.7%), oliguria 73 (20.3%), ascites 25 (6.9%), pleural effusion 23(6.4%), and lethargy 13 (3.6%). HCT>20% with concomitant platelet count <50,000/mm3 was seen in 48(13.3%) cases and severe

thrombocytopenia (platelet count<20,000/mm3) in 16(4.4%) cases. Shock was the most common presentation in severe dengue infection and was seen in 146 children (40.5%). Among them compensated shock was present in 121 cases (82.9%) and 25 children (17.1%) had decompensated shock. Six children (1.7%)

had fluid refractory shock and required inotropic support. 34 children (23.3%) with shock had bleeding. Dengue with shock without bleeding was the most common mode of presentation and it was difficult to categorize them as dengue hemorrhagic fever as per the 1997 WHO guidelines.

Table 1: Univariate analysis of early warning signs in children with dengue fever.

Warning signs	Severe Dengue (146)	Non-severe dengue (214)	Total	Univariate OR(95% CI)	P-value
Pain abdomen	72(51.8)	67(48.2)	139(38.6)	2.1(1.38-3.29)	<0.001**
*Bleeding	38(63.3)	22(36.7)	60(16.7)	3.0(1.72-5.51)	<0.001**
*Persistent vomiting	131(47.5)	128(52.5)	276(76.6)	5.8(3.26-10.96)	<0.001**
*No clinical improvement>7 days	25(83.3)	05(16.7)	30(8.3)	8.6(3.3-25.8)	<0.001**
*Detoriation at time of defervescence	48(80)	12(20)	60(16.7)	8.1(4.24-16.73)	<0.001**
*Cold & clammy Extremities	135(89.4)	16(10.6)	151(41.9)	146.8(68.14-340.40)	<0.001**
*Poor peripheral pulses	126(86.3)	20(13.7)	146(40.5)	59.8(31.5-118.5)	<0.001**
*Hypotension at admission	99(90)	15(10)	110(30.5)	27.5(14.96-53.23)	<0.001**
*Lethargy	9(69.2)	4(30.8)	13(3.6)	3.4(1.05-13.06)	0.02**
*Restlessness	69(77.5)	20(22.5)	89(24.7)	8.6(4.96-15.45)	<0.001**
*Giddiness	74(93.7)	5(6.3)	79(21.4)	42.4(17.59-123.1)	<0.001**
*Oliguria	63(86.3)	10(13.7)	73(20.3)	15.3(7.72-32.93)	<0.001**
*Hepatomegaly	110(55)	90(45)	200(55.5)	4.1(2.64-6.72)	<0.001**
*Pleural effusion	18(78.3)	5(21.7)	23(6.4)	5.8(2.20-18.03)	0.001**
*Ascites	21(84)	04(16)	25(6.9)	8.7(3.12-30.46)	0.0005**
*HCT>20%+PLT<50,000/mm ³	36(75)	12(25)	48(13.3)	5.4(2.78-11.36)	0.003**
Severe thrombocytopenia (Platelet count<20,0000/mm³)	14(87.5)	02(12.5)	16(4.4)	11.3(2.88-74.77)	0.0003

^{*}Data are in numbers (%), odds ratio, 95% CI, **P<0.05 significant

Bleeding manifestations were present in 60 children (16.7%), which mainly included gum bleeding 27(45.0%), melena 27(45.0%), petechiae 25(41.7%), epistaxis 20(33.3%), hematemesis 5(8.3%), pulmonary bleed 4(6.6%) and intracranial bleed 2(3.3%). Melena was the most common form internal bleeding in severe-dengue infection. Tourniquet test was positive in 35 cases (9.7%) and showed significant association with severe dengue infection (Table 2).

Severe dengue infection with complications in the form of severe organ involvement was seen in 25(6.9%) cases. Impaired consciousness at the time of admission in 8 cases (2.2%) and out of them four (66%) had poor outcome. Acute kidney injury and refractory shock were present in six cases (2.0%). Myocarditis, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage and disseminated intravascular coagulopathy were observed in 5 cases (1.4%). Myositis, fulminant hepatic failure and pericardial effusion were seen in two cases (0.7%).

The Dengue NS1Ag was positive in 307 cases (85.3%), 53 children (14.7%) were negative for NS1Ag assay and positive for IgM MAC ELISA and IgG was positive in 20 cases (5.5%). Anemia (Hb<10gm/dl) was seen in 96 cases (26.7%). Mean hematocrit in the severe dengue and non-severe dengue were 43.2 (4.4) and 38.7 (4.4)

respectively. Hematocrit value>40 was seen in 147 (40.8%) cases (Table 2). Leucopenia (TLC<4000/mm3) was seen in 78 (21.7%) cases and among them severe and non-severe dengue were 36 (46.1%) and 38 (53.9%) respectively and was not statistically significant (P=0.176).

Thrombocytopenia was present in 271 (75.3%) cases. 16 (4.4%) children had platelet counts less than 20,000/mm3, 47 (13.1%) children were between 20,000-50,000/mm3, 85 (23.6%) children had platelet count between 50,000-1,00,000/mm3, 139 (38.6%) children had platelet count between 1-1.5 lakh/mm³ and 73 (20.3) children were >1.5 lakh/mm3. Bleeding manifestations were present in 24 (40.0%), 13 (12.6%), 12 (20.0%) and 11 (18.3%) cases with platelet count between $<\!50,\!000/mm^3, \quad 50,\!000\text{-}100,\!000/mm^3, \quad 1\text{-}150,\!000 \quad and \\ >\!150,\!000/mm^3 \quad respectively. \quad USG \quad abdomen \quad showed$ features of gall bladder wall edema in 35 cases (9.7%) during the critical phase of illness and out them 31 cases (88.6%) had severe dengue infection. Deranged liver function test (SGOT and SGPT>150 IU/L) was abnormal in 29 cases (8.1%) and among them 21 cases (72.4%) had severe dengue infection (Table 2).

The early clinical warning signs at the time of admission that were significantly associated with severe dengue infection on univariate analysis were pain abdomen, persistent vomiting, restlessness, giddiness, oliguria, bleeding, hepatomegaly, pleural effusion, ascites, no clinical improvement>7 days, clinical detoriation at the

time of defervescence, cold and clammy extremities, poor peripheral pulses, hypotension at admission, HCT>20% with concomitant platelet count<50,000/mm³ and severe thrombocytopenia(Platelet count<20,000/mm³ (Table 1).

Table 2: Univariate analysis of the clinical variables not enlisted as warning signs.

Warning signs	Severe dengue (146)	Non-severe dengue (214)	Total (360)	Univariate OR (95% CI)	P-Value
*Age > 6 years	112(51.4)	106(48.6)	218(60.5)	3.3(2.10-5.39)	< 0.001
*Retro-orbital pain	81(52.9)	72(47.1)	153(42.5)	2.4(1.59-3.79)	<0.001**
*Palmar erythema	84(45.4)	101(54.6)	185(51.4)	1.5(0.99-2.32)	<0.027**
*Splenomegaly	43(57.3)	32(42.7)	75(20.8)	2.3(1.41-4.00)	0.001**
*Joint pain	51(54.8)	42(45.2)	93(25.8)	2.1(1.35-3.55)	0.001**
*Right hypochondriac pain	35(63.6)	20(36.4)	55(15.3)	3.0(1.68-5.62)	0.002**
*Epigastric tenderness	64(76.2)	20(23.8)	84(23.3)	7.5(4.32-13.48)	<0.001**
Facial flush	51(51)	49(49)	100(27.8)	1.8(1.13-2.88)	0.005**
Lymphadenopathy	67(63.8)	38(36.2)	105(29.2)	3.9(2.43-6.36)	0.299
*Melena	22(81.5)	5(18.5)	27(7.5)	7.3(2.84-22.37)	<0.001**
*Tourniquet test	25(71.4)	10(28.6)	35(9.7)	4.1(1.97-9.43)	<0.001**
Thrombocytopenia (<1,50,000/mm ³)	126(46.5)	145(53.5)	271(75.3)	2.9(1.73-5.29)	<0.001
Hemoconcentration(HCT>40)	101(68.7)	46(31.3)	147(40.8)	8.1(5.10-13.26)	<0.001
Leucopenia(TLC<4000/mm ³)	36(46.1)	38(53.9)	78(21.7)	1.5(0.90-2.54)	0.06
Hyponatremia (Sodium<130 Meq/L)	16(88.9)	2(11.1)	18(5.0)	12.9(3.35-84.58)	<0.001
GB wall edema on USG	31(88.6)	2(11.4)	35(9.7)	28.3(7.80-178.8)	<0.001
*Deranged LFT (SGOT & SGPT>150 IU)	21(72.4)	8(27.6)	29(8.1)	4.3(1.88-10.61)	<0.01
Secondary infection (Dengue IgG Ab +ve)	18(90)	02(10)	20(5.5)	14.8(3.88-95.87)	<0.001

^{*}Data are in numbers (%), odds ratio, 95% CI, P<0.05 significant, LFT: liver function test; SGOT-serum glutamate oxaloacetate transferase; SGPT-serum glutamate pyruvate transferase

Table 3: Multivariate analysis of clinical variables for severe dengue infection.

Warning signs	Odds ratio (OR)	Adjusted Odds ratio (AOR)	P-value
*Pain abdomen	2.1 (1.38-3.29)	1.2 (1.06-8.49)	< 0.001
Persistent vomiting>48hrs	5.8 (3.26-10.96)	0.05 (0.30-3.58)	< 0.001
*Oliguria	15.3 (7.72-32.93)	2.6 (2.42-61.12)	< 0.001
*Hepatomegaly	4.1 (2.64-6.72)	1.2 (1.31-8.98)	< 0.001
Ascites	8.7 (3.12-30.46)	0.8 (0.17-34.18)	< 0.001
Thrombocytopenia at admission	2.9 (1.73-5.29)	1.0 (0.92-7.96)	<0.001*
*HCT>20%+PLT<50,000/mm ³	5.4 (2.78-11.36)	3.7 (2.47-7.69)	< 0.001
*Secondary infection	14.8 (3.88-95.87)	5.1 (5.1-6122.78)	< 0.001
Severe thrombocytopenia at admission (Platelet count<20,000/mm ³)	11.3 (2.88-74.77)	1.2 (0.91-7.96)	0.0003
*GB wall edema	28.3 (7.80-178.8)	2.6 (1.05-206.29)	< 0.001
*Hyponatremia (serum sodium<130 Meq/L)	12.9 (3.35-84.58)	3.9 (1.53-1603.10)	< 0.001
*Hypotension at admission	27.5 (14.96-53.23)	4.4 (1.53-21.37)	< 0.001

^{*} Data are in n (%), OR, AOR, 95% CI, P<0.05 significant. OR: odds ratio; AOR: Adjusted odds ratio; CI: confidence interval; GB: Gall bladder

The clinical variables at admission that were significantly associated with severe dengue infection but not enlisted as warning signs in the revised guidelines were Age >6 yrs, retro-orbital pain, palmar erythema, joint pain, splenomegaly, positive tourniquet test, right hypochondriac pain and epigastric tenderness (Table 2).

The laboratory parameters most commonly associated with severe dengue infection on univariate analysis were thrombocytopenia (Platelet count< 1, 50,000/mm³) at admission, hematocrit (HCT) > 20% with concomitant platelet count<50,000/mm³ on admission, severe thrombocytopenia (platelet count <20,000/mm³),

HCT>40, deranged liver function tests (LFTs), gall bladder wall edema, secondary infection (positive dengue IgG antibody), and hyponatremia (Table 1 and 2). On multivariate analysis, it was seen that that pain abdomen, oliguria, hepatomegaly, gall bladder wall edema, hypotension at admission, secondary infection and HCT>20% with concomitant platelet count <50,000/mm³ were the most common early warning signs that were significantly associated with severe dengue infection (Table 3)

Platelet transfusion was given in 23 children (6.8%) with severe dengue infection and out of them 13 children (56.5%) had a platelet count <20,000/mm3; whereas 10 children (43.5%) had platelet count in the range of 20,000-50,000/mm3. Apart from platelet transfusion blood transfusion was given in 11 (3.1%) cases, fresh frozen plasma in 6 (1.7%) cases, colloids in 3 (0.8) intravenous fluids in 194 (53.9%) cases, and inotropes in 6 (1.7%) cases. There were six deaths (1.7%) and out of them four presented with impaired consciousness (66.6%) at admission with GCS <8. The common causes for poor outcome (deaths) were multiorgan failure, encephalopathy, DIC, and refractory shock. The mean duration of hospital stay was 8.1(2.3) days and the mean time to death was 2.7 (2.3) days.

DISCUSSION

This study was an attempt to identify and evaluate the role of early warning signs at the time of admission that were predictive of development of severe dengue infection. We found that most commonly affected age group were children > 6 years of age and were at risk to develop severe dengue infection. As per the 2009 WHO revised guidelines, infants and young children are high risk group to develop severe dengue infection contrary to our findings. The probable factors for higher age to be affected were increased exposure to mosquito bites, active viral replication, and secondary infection as was few previous reports. 2-5

Among the enlisted warning signs as per revised world health organization 2009 guidelines we found persistent vomiting, pain abdomen, hepatomegaly, spontaneous bleeding, giddiness, oliguria, cold and calmy extremities, hypotension, spontaneous bleeding, pleural effusion, ascites and HCT>20% at admission with concurrent PLT<50,000/mm³ were the most common predictors of severe dengue infection.

The clinical and laboratory variables which were significantly associated with severe dengue infection but not enlisted as warning signs in the revised guidelines were Age > 6 years, right hypochondriac pain, epigastric tenderness, joint pain, impaired consciousness, retroorbital pain, gall bladder wall edema, positive tourniquet test secondary infection and hyponatremia. In present study, shock was the most common form of presentation in severe dengue infection and was present in 40.5% in

comparison to the previous studies by Ratageri et al., Aggarwal et al., where it was present in 22% and 33%, respectively.^{6,7} The most common warning signs that were of predictors of development of shock were cold and clammy extremities, giddiness, persistent vomiting and oliguria. The most common mode of presentation of severe dengue infection was a peripheral circulatory failure without bleeding, and there was difficulty in classifying them as DHF as per 1997 WHO classification as most cases failed to fulfil all the four criteria of fever, haemorrhagic phenomenon, thrombocytopenia, hemoconcentration. They were sub-classified as dengue fever with bleeding without shock and dengue fever associated with peripheral circulatory failure without bleeding based on the revised 2009 WHO guidelines for dengue fever.1

Bleeding manifestations as an early warning sign was significantly associated with severe dengue infection and was more common in children > 6 years of age similar to previous studies.^{2,3} Melena constituted the most common form of internal bleeding in present study and unlike previous studies where hematemesis was most common.4,5 The tourniquet test in present study was positive in 9.7% and was lower compared to the previous studies by Narayanan et al and Gomber et al where it was 26.4% and 25.5% respectively.^{4,5} The tourniquet test in present study did not correlate well with bleeding manifestations or with thrombocytopenia but was significantly associated with severe dengue infection. There was poor correlation between tourniquet test, bleeding manifestations, and thrombocytopenia in nonsevere dengue infection as bleeding occurred even with normal platelet counts. The correlation between thrombocytopenia and bleeding was more common in severe dengue infection than non-severe dengue infection. Hence, platelet transfusion was given only those cases which had severe dengue infection, significant bleeding and severe thrombocytopenia.

The signs of plasma leakage in the form of pleural effusion, ascites, and HCT> 20% with concomitant platelet count < 50,000/mm³ were found to be significant predictors of shock in present study and similarly reported by Chacko and Subramanian.² The early clinical warning signs that later developed signs of plasma leakage were persistent vomiting, giddiness and oliguria and were seen to significantly associated with severe dengue infection which has not been previously reported.

Hepatomegaly is a common finding and one of the warning signs in dengue fever. We found significant correlation to the presence of hepatomegaly with severe dengue infection as was found in other studies. ^{2,3,6} Abnormal LFTs were significantly associated with shock in this study that is contrary to the previous studies. ^{2,4,5} Acute liver injury is a severe complicating factor in dengue, predisposing to life-threatening complications like internal hemorrhages, disseminated intravascular coagulation (DIC) and encephalopathy. The presence of

ascites, abnormal LFT with raised SGOT were more significantly associated with severe dengue in present study similar to the previous studies.⁸⁻¹⁰

Pain abdomen and persistent vomiting were the most common abdominal symptom and was considered as clinical warning sign associated with severe dengue infection and are similar to the few previous studies.^{2,3} The association of right hypochondriac pain and epigastric tenderness was significantly seen with severe dengue infection and has not been reported previously. As a clinician, one must be very vigilant about the symptoms of pain in abdomen and vomiting as these are the early warning signs before worsening to severe dengue. General practitioners may be confused as hepatitis, whereas surgeons might think in terms of acute abdomen. If observed and managed in time most of the complications of dengue can be prevented. Splenomegaly was seen in 20.8% and was significantly associated with severe dengue infection and such higher percentage was similarly observed in study by Faridi et al.¹¹

Altered sensorium and seizures at the time of admission was an ominous warning sign for mortality in children with severe dengue infection in present study as four out of six cases (66%) had expired and in our experience should enlisted as a warning sign for severe dengue infection. Pancharoen in his study, reported altered sensorium as the most common neurological finding followed by seizures and observed these findings in 75% of patients with severe dengue infection. 12 Rigua-Perez et al and similar previous studies have reported a high proportion of impaired consciousness at presentation and during disease progression showing with and multi-organ involvement high mortality. 13 Dengue infection can cause neurological manifestations secondary to cerebral hypoperfusion due to shock, encephalopathy, hepatic dysfunction, metabolic derangements such hyponatremia and hypoglycemia, or rarely due to acute disseminated encephalomyelitis or Gullian-Barre syndrome. 14

The earliest hematological abnormality is a progressive decline in total leukocyte count in patients with dengue infections. A leucopenia <5000mm³ was reported in their studies by Gupta et al and Chacko et al as an early predictor of dengue hemorrhagic fever.^{2,3} We could not find similar association with severe dengue infection in present study. In dengue endemic areas, positive tourniquet test and leukopenia (WBC<5000cells/mm³) help in making early diagnosis of dengue infection with a positive predictive value of 70-80%.^{26,27}

Thrombocytopenia (Platelet count <1,50,000) at the time of admission and severe thrombocytopenia (platelet count < 20,000/mm³) were significant predictors of shock and similar to the previous studies. Nyugen et al showed HCT>20% and severe thrombocytopenia an important earliest predictor of severe dengue infection. In present study signs of plasma leakage in the form of pleural

effusion, ascites and HCT>20 % with concomitant platelet count<50,000/mm³, at the time of admission found to be significant predictors of severe dengue infection and has been reported in the previous studies.^{2,3} In present study the presence of hemoconcentration with severe thrombocytopenia gave important clues towards diagnosis of severe dengue infection as illustrated in the previous studies.¹⁹

Hyponatremia was significantly associated with shock in present study and was similar to the previous studies.² Secondary infection was significantly associated with shock in present study. Weichmann et al. in their study showed that secondary infection was significantly associated with shock. During secondary infection T-cells become activated due to interactions with infected monocytes which induce plasma leakage by release of cascade of cytokines such as interferon-gamma, interleukin 2, and tumor necrosis factor-alpha therefore predisposing to shock.²⁰

Gall bladder wall edema on ultrasound preceded plasma leakage in present study was significantly associated with severe dengue and was similar to the previous studies.^{21,22} Gall bladder wall thickening (GBWT) had a direct correlation with dengue severity and was used as an early warning signs for plasma leakage in present study. GBWT in severe dengue infection was first reported by Pramulijo et al. in 1991.²³ There is considerable association between GBWT and the severity of dengue infection and can be used as criterion for patient hospitalization, monitoring and in selection of patients with higher risk for progressing to shock as has been reported in the previous studies.²¹⁻²³ The probable pathogenesis of GBWT as an early indicator of plasma leakage are increased capillary permeability secondary to release of cytokines and inflammatory cells, endothelial damage due to virus, immune complex deposition on capillary endothelium and decreased intravascular osmotic pressure.24

The predominant presentation in children with shock was peripheral circulatory failure without bleeding which made it difficult to classify dengue hemorrhagic fever as per the WHO 1997 guidelines. ²⁵ As per the WHO revised guidelines 2009 we termed them as severe dengue with peripheral circulatory failure without bleeding rather than dengue hemorrhagic fever. ¹ It also indicated a change in pattern of presentation of dengue fever during the recent epidemics at Puducherry.

The early clinical warning signs were far more important than the laboratory parameters in present study.

Even though the warning signs enlisted in the revised WHO guidelines for dengue fever were predictors for development of severe dengue infection, there were clinical and laboratory variables not enlisted as warning signs as per the WHO guidelines but were significantly associated with severe dengue infection in present study.

Our experience suggests that there is a need for to relook at the list of early warning signs as per world revised WHO guidelines for dengue fever.

There are several limitations to the present study. The study is retrospective analysis of dengue fever cases from a single centre and included only those cases which were admitted in the hospital. We derived the early warning signs in children with dengue fever by univariate and multivariate analysis and coefficient of binary logistic regression to overcome the confounding variables. Another limitation of the study that we could not derive the average duration between the onset of individual warning signs and appearance of severe dengue infection. There were clinical variables which had statistical significance but with wider confidence intervals, which indicated a relatively smaller sample size. A large multicentric prospective study with wider sample size and population focusing on role of warning signs would be ideal.

CONCLUSION

The early identification of the preceding warning signs, timely intervention and vigilant monitoring can reduce the morbidity and mortality in children with severe dengue infection. Since apart from the enlisted warning signs there were other clinical variables that were also associated with severe dengue infection, the list of warning signs in the revised guidelines needs to be expanded.

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