Original Article

A study on predictors of severe dengue in pediatric patients in a tertiary care hospital in Telangana

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ABSTRACT

Background: Dengue is an emerging arthropod borne disease with increasing incidence in recent years in several countries, especially India. Early recognition of progression of disease helps in triage and timely management of fluids to decrease mortality. **Objective:** The objective of the study was to identify the predictive factors for severe dengue in pediatric patients for hospitalization for close monitoring. **Methods:** This was a prospective observational study conducted in the department of pediatrics in a tertiary care hospital in Mahbubnagar from June 2019 to May 2020. One hundred and four children between the age group of 0 and 15 years with probable dengue symptoms who were willing to get admitted were included in the study cohort. Thorough history and clinical examination, basic laboratory investigations such as complete blood picture, hematocrit, liver function tests, renal function tests (RFTs), serum electrolytes, serum ferritin, and coagulation profile were done as needed. All the patients were grouped into two groups – non-severe dengue (dengue fever without warning signs and dengue fever with warning signs) and severe dengue as per the World Health Organization guidelines. All the variables were analyzed using SPSS software. **Results:** Out of 104 confirmed cases, majority of the admissions were in 5–10 years age group (51.9%). Male children were 61.5%. Mean duration of hospitalization was 4.79±2.96 days. Fever (97.1%) was the most common symptom followed by anorexia (86.5%) and lethargy (82.7%). Symptoms such as lethargy, vomiting, abdominal pain/epigastric tenderness, epistaxis, edema, and altered sensorium were more commonly associated with severe dengue. Hepatomegaly (53.9%) was the most common clinical sign followed by epigastric tenderness (58.7%). Hepatomegaly, splenomegaly, ascites, gallbladder edema, pleural effusion, low pulse pressure, hypotension, oliguria, and significant gastrointestinal bleeds were more common in severe dengue group. Platelet count <50,000/mm^3, increase in hematocrit more than 20% from baseline, raised transaminases, raised ferritin, decrease in serum sodium, decrease in serum albumin, abnormal coagulation profile, and abnormal RFTs were significantly associated with severe dengue. Mean platelet recovery time was 3–5 days. **Conclusion:** Dengue is a dynamic disease and progression of dengue with or without warning signs into severe dengue can be appropriately identified by close monitoring of certain clinical signs and symptoms.

Key words: Monitoring, Non-severe dengue, Severe dengue, Triage, Warning signs

Dengue is an arthropod borne viral disease which has a huge impact on human health as well as the global and national economies. It is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature, relative humidity, and unplanned rapid urbanization [1]. A total of 390 million dengue virus infections occur per year of which 96 million manifests clinically with varying severity [2]. A study on the prevalence of dengue estimates that 3.9 billion people are at risk of infection with dengue viruses. Despite a risk of infection existing in 129 countries [3], 70% of the actual burden is in Asia [2]. In 2020, dengue continues to affect several countries, with reports of increase in the numbers of cases in number of countries including India.

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Bhatt *et al*. showed a discrepancy between reported and modeled dengue incidence, which was particularly high for India. According to their estimates, India contributed 34 of 96 million apparent global dengue infections, a number which stands in stark contrast to the 12,484 reported cases from India to the World Health Organization (WHO) in the same year. Such a mismatch was also reported for India in another study, in which the actual numbers of dengue cases were 282 times the number reported by the national vector-borne disease control program [4].

Dengue is a systemic and dynamic disease. After the incubation period, the illness begins abruptly and is followed by the three phases; febrile, critical, and recovery phase [5]. The WHO classifies dengue into two major categories: Dengue (with/without warning signs) and severe dengue. This subclassification

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of dengue with or without warning signs is designed to aid the health practitioners triage patients for hospital admission, ensuring close observation, and minimizing the risk of developing the more severe dengue [6].

Laboratory diagnosis can be made by detection of NS1 antigen (reverse transcription polymerase chain reaction, commercially produced rapid diagnostic tests) or serological methods for the detection of immunoglobulin (Ig) M, IgG antidengue antibodies by enzyme-linked immunosorbent assay (ELISA), or card tests. There is no specific treatment for dengue. Maintenance of the patient's body fluid volume is critical to severe dengue care. The present study is aimed at studying the variable clinical presentations of dengue in pediatric patients as well as assessing the various predictive and prognostic markers for progression to severe dengue at primary level so that appropriate fluid management and timely referral for better care can be done to decrease mortality.

METHODS

This was a prospective observational study conducted in the department of pediatrics in a tertiary care hospital in Mahbubnagar from June 2019 to May 2020. Children between the age group of 0 and 15 years with probable dengue symptoms who were willing to get admitted were tested for NS1 antigen or IgM antibodies by rapid card test, ELISA depending on day of presentation. A total of 104 children were included in the study cohort. Informed consent from parent or accompanying guardian was taken. Ethical committee clearance was taken. Children between the age group of 0 and 15 years were included in study. Those with preexisting chronic illness or any concurrent fever causing illness such as malaria, typhoid, and urinary tract infections were excluded from the study.

Thorough history was taken as per the preformed and detailed clinical examination was done. Basic laboratory investigations such as complete blood picture, hematocrit, liver function tests, renal function tests (RFTs), serum electrolytes, serum ferritin, coagulation profile, and blood sugar were done as needed. Serial blood investigations, chest X-ray, and ultrasound (USG) abdomen were done wherever necessary. All the patients were grouped into two groups – 77 non-severe dengue patients (dengue fever without warning signs and dengue fever with warning signs) and 27 severe dengue patients.

All the variables were analyzed using SPSS software. Independent variables were compared between non-dengue and dengue group using Chi-square test and $p<0.05$ is taken as statistically significant.

RESULTS

Out of 104 confirmed cases, majority of admissions were in 5–10 years age group. Mean age of admission was 7.30±4.26 years. Minimum age of admission in the present study was 5 months. Severe dengue patients were also more noted in 5–10 years age group though value is not statistically significant (p=0.465). Male children were 64 (61.5%) and female children were 40 (38.5%). Most of the children were admitted for 2–7 days. Mean duration of hospitalization was 4.79±2.96 days (Table 1).

Symptoms such as lethargy, vomiting, abdominal pain/epigastric tenderness, epistaxis, edema, and altered sensorium were more commonly associated with severe dengue. There was no much difference in erythematous rash between two groups but petechial rash was more common with severe dengue and was seen in 11 of them. Although altered sensorium was associated with severe dengue in our study, simple febrile seizure was seen in a 2-year-old child on day 1 of fever, the child recovered without any warning signs or severe manifestations. Jaundice was seen in two patients with severe dengue. All clinical manifestations are listed in Table 2.

Hepatomegaly, splenomegaly, ascites, gallbladder (GB) edema, pleural effusion, low pulse pressure, hypotension, oliguria, and significant gastrointestinal (GI) bleeds were more common in severe dengue group. In non-severe dengue group, ascites was more frequently noticed in infants. Both patients in severe dengue group who presented without fever had hypotension at the time of admission (Table 3).

Table 1: Age-wise distribution of dengue cases

Age	Total (n=104)	Non-severe dengue (n=77)	Severe dengue (n=27)
<1 year	8 (7.7)	7 (9.1)	1 (3.7)
1–5 years	22 (21.1)	14 (18.2)	8 (29.6)
5–10 years	54 (51.9)	42 (54.5)	12 (44.4)
10–15 years	20 (19.2)	14 (18.2)	6 (22.2)

Table 2: Clinical manifestations of cases

Symptom/n (%)	Total (n=104)	Non-severe dengue (n=77)	Severe dengue (n=27)	p-value
Fever	101 (97.1)	76 (98.7)	25 (92.6)	0.102
Anorexia	90 (86.5)	64 (83.1)	26 (96.3)	0.842
Lethargy/ decreased activity	86 (82.7)	60 (77.9)	26 (96.3)	0.03*
Myalgia/arthralgia	56 (53.9)	38 (49.4)	18 (66.7)	0.12
Rash	34 (32.7)	15 (19.5)	19 (70.3)	<0.0001*
Headache	54 (51.9)	38 (49.4)	16 (59.3)	0.38
Vomiting/nausea	76 (73.1)	52 (67.5)	24 (88.8)	0.03*
Diarrhea	20 (19.2)	12 (15.6)	8 (29.6)	0.11
URI symptoms	5 (4.8)	4 (5.1)	1 (3.7)	0.76
Abdominal pain	40 (38.5)	22 (28.5)	18 (66.6)	0.0005*
Retro-orbital pain	23 (22.1)	15 (19.4)	8 (29.6)	0.27
Epistaxis	8 (7.7)	2 (2.6)	6 (22.2)	0.001*
Jaundice	2 (1.9)	0	2 (7.4)	*
Edema	16 (15.2)	6 (7.8)	12 (44.4)	0.0002*
Altered sensorium	2 (1.9)	0	2 (7.4)	*
Seizures	1 (0.9)	1 (1.2)	0	*

URI: Upper respiratory infection

In our study, hemoglobin, leukopenia (65.4%), and anemia (53.9%) were frequently noticed but did not show significant association with severe dengue. Platelet count <50,000/mm^3, increase in hematocrit more than 20% from baseline, raised transaminases, raised ferritin, decrease in serum sodium, decrease in serum albumin, abnormal coagulation profile, and abnormal RFT were significantly associated with severe dengue. Mean platelet recovery time was 3–5 days in patients with <100,000/mm^3 and no difference was seen in both groups (Table 4).

DISCUSSION

Dengue is a dynamic disease. Early recognition of cases progressing to severity helps in appropriate fluid management at primary level as well as timely referral if needed to tertiary care centers. Predictors of severe dengue should be basic investigations as well as easily identifiable clinical signs and symptoms. This study is such an attempt to prognosticate the dengue fever. A total of 104 patients were included in the study who were grouped as non-severe and severe as per the WHOs operational guidelines for diagnosis and treatment [5] and handbook for clinical management of dengue [6]. Results reported by our study were similar to the results reported by Mishra *et al*. [7] and Sheela *et al*. [8] in terms of number of patients in both groups.

Table 3: Signs of dengue patients

Signs/n (%)	Total (n=104)	Non-severe dengue (n=77)	Severe dengue (n=27)	p-value
Hepatomegaly	56 (53.9)	35 (45.5)	21 (77.8)	0.003*
Splenomegaly	8 (7.7)	2 (2.6)	6 (22.2)	0.001*
Lymphadenopathy	12 (11.5)	8 (10.4)	4 (14.8)	0.53
Eye signs	21 (20.2)	14 (18.2)	7 (35)	0.39
Ascites	16 (15.4)	3 (3.9)	13 (48.1)	<0.001*
Epigastric tenderness	61 (58.7)	41 (53.2)	20 (74.1)	0.06
Pleural effusion	15 (14.4)	2 (2.6)	13 (48.1)	<0.001*
Low pulse pressure (≤20 mmHg)	12 (11.5)	0	12 (44.4)	*
GB edema (USG finding)	24 (23.1)	8 (10.3)	16 (59.3)	<0.001*
GI bleed	10 (9.6)	0	10 (37.03)	*
Oliguria	8 (7.7)	1 (1.2)	7 (25.9)	<0.001*
Hypotension	8 (7.7)	0	8 (29.6)	*

USG: Ultrasound, GI: Gastrointestinal, GB: Gallbladder

Table 4: Laboratory investigations of dengue cases

Investigations/n (%)	Total (n=104)	Non-severe dengue (n=77)	Severe dengue (n=27)	p-value
Anemia	56 (53.9)	40 (51.9)	16 (59.3)	0.512
Leukopenia<4000/mm^3	68 (65.4)	50 (64.9)	18 (66.6)	0.87
Leukocytosis> 11,000/mm^3	20 (19.2)	13 (16.9)	7 (25.9)	0.3
Platelets<50,000/mm^3	24 (23.1)	8 (10.3)	16 (59.3)	<0.001*
Raised hematocrit≥20%	26 (25)	6 (7.8)	20 (74.1)	<0.001*
Abnormal coagulation profile	8 (7.7)	0	8 (29.6)	*
Hypoalbuminemia≤ 2.5 mg/dl	18 (17.3)	10 (12.9)	8 (29.6)	<0.001*
Hyponatremia≤130 meq/	16 (15.4)	7 (9.1)	9 (33.33)	0.003*
SGOT≥200U	26 (25)	6 (7.8)	20 (74.1)	<0.001*
SGPT≥200U	24 (23.1)	4 (5.2)	20 (74.1)	<0.001*
S. ferritin>1000	29 (27.9)	8 (10.3)	21 (77.8)	<0.001*
Abnormal RFT	4 (3.8)	0	4 (1.5)	*

RFT: Renal function test, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase

We observed that majority were from 5 to 10 years age group. This may be due to more outdoor activities by children of this age group and relatively more uncovered area and hence more prone for mosquito bites [9-12]. Male children (61.5%) were more commonly affected by dengue fever than female children. Gender difference in incidence may be also due to difference in clothing pattern and degree of outdoor activities. Similar observations were made by Mishra *et al*. [7] and Majeed *et al*. [13]. However, Nandwani *et al*. [12] noted that severe dengue and complications were more in female children.

Symptoms such as lethargy, vomiting, abdominal pain, epistaxis, edema, and altered sensorium were more commonly associated with severe dengue while headache, myalgia, upper respiratory symptoms, diarrhea, retro-orbital pain, and rash did not show much differences between both the groups and fever was common in both. Similar findings in severe dengue regarding fever, headache, vomiting, and oliguria were observed by by Somasundaram *et al*. [14]. However, they also observed that diarrhea is more common in severe dengue but our study did not support that. A study by Jayarajah *et al*. [15] also showed similar association of abdominal symptoms and signs more commonly with dengue hemorrhagic fever (DHF) rather than dengue fever. In another study by Padhmanabhan *et al*. [16], fever (90.1%) and rash (27.2%) were more frequently associated with severe dengue which did not correlate with our findings. In Fernandez *et al*. [17] study, headache and petechial rash were negatively associated with severe dengue whereas in our study, petechial rash was more associated with severe dengue. In a study, Kumar *et al*. [18] observed vomiting in 68.9% and abdominal pain in 62.5% of severe dengue cases; however, altered sensorium was seen in 7.8% which was much higher than our study.

In our study, we have noticed hepatomegaly, splenomegaly, ascites, and pleural effusion, and low pulse pressure, GB edema on USG, GI bleed, oliguria, and hypotension. All these findings were significantly associated with severe dengue. Anand *et al*. [19] reported hepatomegaly in 57% of cases which is similar to our study but splenomegaly was seen only in children with concurrent malaria or Gram-negative infection. As per studies done by Sastry *et al*. [20] and Sahana *et al*. [21], more frequent association of organomegaly and fluid collection were reported in severe dengue than our study. Mishra *et al*. [7] reported more GI bleed (76.9) in severe dengue group than ours.

We noticed anemia, leukopenia, and leukocytosis but all these three factors did not have significant association with severe dengue. Thrombocytopenia (<50,000/mm^3) and hematocrit rise ≥20% from baseline or mean of population were also noted in our study. Nandwani *et al*. [12] observed that low hemoglobin, high total leukocyte count (TLC), and low platelet were associated with severe outcome. A study by Tanner *et al*. [22] from Singapore emphasized that platelet count <50,000/mL early in the illness associated with poor prognosis during the clinical course.to be changed to - In a study by Srilanka by Kularatnam *et al*. [23], a total leucocyte count of less than 2.6×10^9 /L and platelet count less than 100×10^9 /L at day 2.5 was highly suggestive of child progressing into DHF.

In our study, we have observed abnormal coagulation profile, hypoalbuminemia, hyponatremia, raised transaminases, raised serum ferritin, and abnormal RFT. All these parameters were significantly associated with severe dengue. Studies by Kularatnam *et al*. [23], Mishra *et al*. [7], Sheela *et al*. [8], Kumar *et al*. [18], and Somasaundaram *et al*. [14] agreed with the association of raised liver transaminases with severe dengue fever. Jayarajah *et al*. [15], reported that low white blood cell (WBC) and low platelet counts to be significantly associated with DHF but liver enzyme derangement did not predict DHF.

Mishra *et al*. [7] and Padmanabhan *et al*. [16] stated that raised hematocrit was statistically not significant in severe dengue which does not correlate with our study. Sheela *et al*. [8] stated in their study that when non-severe dengue and severe dengue were compared, platelet count, serum sodium, albumin, serum glucose, RFT, and coagulation profile as predictors which correlates with our study. Similar observations were made by Kumar *et al*. [18]. Somasaundaram *et al*. [14] noted that low hemoglobin, low platelet count were well associated with severe dengue but not total WBC and serum albumin.

This was a single-center tertiary care study and hence there could be a lot of selection bias and observer bias in the study cohort. Baseline value of hematocrit in the first 3 days was not available for all the cases where mean population hematocrit was taken. Hence, results presented here need to be reviewed in this context and further larger prospective studies will be needed to further validate the findings observed in this study.

CONCLUSION

Identification of progression of dengue from one phase to another phase can be appropriately done by close monitoring of certain clinical signs and symptoms. Even dengue without warning signs can rapidly progress to severe dengue. Hence, clinicians should have a good knowledge of predictors and prognostic factors of severe dengue. Independent predictors found to be abdominal pain, vomiting or nausea, extreme lethargy or loss of daily activity, mucosal bleeds, GI bleeds, altered sensorium, hepatomegaly, splenomegaly, clinical fluid accumulation, oliguria, low pulse pressure, GB wall edema on USG, raised transaminases, raised hematocrit, raised ferritin, platelets <50,000/mm^3, hypoalbuminemia, hyponatremia, and abnormal coagulation profile.

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