# **Original Article**

## **Dengue - should we look for confirmation?**

### Vedavyasa Srigade, Koteshwar Bingi

From Department of Pediatrics, Niloufer Hospital, Osmania Medical College, Hyderabad, Telangana, India

**Correspondence to:** Vedavyasa Srigade, 1-1-405/8/1, Near St. Gregorios Cathedral, Hyderabad - 500 080, Telangana, India. Phone: +91-9849939657. E-mail: vsrigade@gmail.com

Received – 28 September 2016

Initial Review - 17 October 2016

Published Online – 03 December 2016

## ABSTRACT

**Background:** Children are at great risk of dengue infection and mortality. Pediatric dengue management needs early identification and timely intervention. **Objective:** Evidence for case management based on clinical diagnosis without waiting for confirmation is aimed at in this study. **Methods:** Retrospective medical record review of pediatric clinical and confirmed dengue cases was done. Children admitted during 6 months in 2015 at Institute of Child Health, Niloufer Hospital, Hyderabad, were included in the study. 3 demographic, 32 symptom, 24 sign, and 24 investigation data were collected. Proportions of individual findings of the total number of patients in the group were compared between clinical and confirmed dengue groups. **Results:** Of the 13,750 admissions, 282 serologically confirmed dengue cases, 407 clinical dengue cases, 4 confirmed dengue deaths, and 24 clinical dengue deaths, making a total of 717 patient data were analyzed. Case fatality rate was 4.06% (95% confidence interval: 2.56-5.57). Except 9 out of 83 parameters, no significant differences of proportions between the groups were present. Age <5 years, seizures, altered sensorium, bradycardia, and systolic blood pressure <70 mmHg were significantly associated with increased mortality in dengue on logistic regression. **Conclusions:** Clinical diagnosis in the light of epidemiology, using acute pain in right hypochondrium, malena, tender hepatomegaly, centrifugal blanchable flushing, and hypotension as definite pointers of dengue avoids vagueness and is sufficient to treat dengue with escalation of fluid therapy as needed and with other supportive measures without waiting for lab support. Currently, available investigations cannot confirm dengue with accuracy in the hour of need, but they should be used for epidemiological purposes.

Key words: Case fatality rate, Clinical features, Confirmation, India, Mortality predictors, Pediatric dengue

Performing the most important and the most rapidly spreading arthropod-borne viral disease of human beings [1]. After an incubation period of 4-10 days, infection by any of the four virus serotypes circulating in India can produce a wide spectrum of clinical manifestations from subclinical to fatal infections [2]. India is in the group of countries with the highest annual dengue infection rate (7.5-32.5 million). Misdiagnosis is contributing to the big disparity between actual and reported numbers of dengue infection [3]. Although clinical studies have reported on dengue in India, these are largely based on the diagnosis made by kits of doubtful specificity and sensitivity [2].

The laboratory diagnosis of dengue is influenced by the methods used, the day post onset of symptoms (DPO), and the ordinal of the infection. Reverse transcription polymerase chain reaction detects dengue virus in the first 5 DPO and is 80-90% sensitive, and >95% specific. A negative result is indeterminate. Dengue NS1 antigen can be detected from 1 DPO to 18 DPO [4]. NS1 enzyme-linked immunosorbent assay (ELISA) tests have 72.8-86% sensitivity and 100% specificity. Sensitivity drops to below 50% by 7 DPO. Sensitivity is higher in primary infection (98.8%) than in secondary infections (83.5%) [5]. NS1 immunochromatography strip's sensitivity is higher in primary

infections (94.7%) than in secondary infections (67.1%) [6]. Antidengue immunoglobulin M (IgM) can be detected from 5 DPO to 2-3 months after the illness. Low titers in secondary dengue result in some false-negative cases. IgM ELISAs have 61.5-99.0% sensitivity and 79.9-97.8% specificity. However, IgM rapid diagnostic tests (RDT) have variable sensitivity (20.5-97.7%) and specificity (76.6-90.6%) [7]. A negative IgG in the acute phase and a positive IgG in the convalescent phase indicate primary dengue. A positive IgG in the acute phase and a 4 fold rise in IgG titer in the convalescent phase indicate secondary dengue [4].

Children are at greater risk of severe dengue than adults [8]. The risk of mortality of children aged 1-5 years due to dengue fever is four-fold higher than in children aged 11-15 years. Dengue case fatality rate (CFR) is 0.8-2.5% [9]. CFR in India was 3-5% compared to 1% in the South-East Asian region, 0.2% in Thailand, and 1.2% in Americas [1]. CFR can be reduced to less than 1% by halting the progression from nonsevere to severe disease by early, intravenous rehydration [1]. Pediatric dengue (PD) poses challenges in its early identification as laboratory diagnosis is influenced by many factors. Misdiagnosis can be fatal as time to death after the onset of shock is 12-36 h, if untreated [8]. More detailed explanation of clinical features such

as abdominal pain, tender hepatomegaly, respiratory distress, shock, and rash is necessary. Strengthening the evidence base, on which support and control planning decisions and their impact are evaluated, is essential in India. Hence, we planned to study clinical and investigational manifestations of PD, both confirmed and unconfirmed, and to compare both the groups for validity of clinical diagnosis.

#### **METHODS**

It was a retrospective study conducted by reviewing medical records of children in the age group 1 month-15 years admitted with clinical dengue and confirmed dengue from June to November 2015 at the Institute of Child Health, Niloufer Hospital, Hyderabad. Medical records were looked for evidence of clinical dengue and serological results. Records without clinical evidence of dengue were excluded from the study. On the basis of evaluation of the history, physical examination and/or full blood count and hematocrit, according to the WHO guidelines, patients were divided into clinical or confirmed dengue groups.

The patients admitted with clinical features of dengue with no serological evidence were included in the clinical dengue group [1]. The patients with serological evidence of dengue (positive NS1 antigen and/or anti-dengue IgM, and/or anti-dengue IgG) along with clinical features of dengue were included in the confirmed group. Positive IgG alone cases with clinical features of dengue were also included in the confirmed dengue group. Patients underwent NS 1 Ag testing with RDT kits at the time of admission while IgM and IgG testing for dengue was done by Alere SD BIOLINE dengue IgG/IgM rapid immunochromatographic test after 5 days of fever.

The data were recorded from case records in predesigned format which included 3 demographic, 32 symptom, 24 sign, and 24 investigation entries. Frequencies of individual findings were tabulated using SPSS software. Proportions of individual findings

| Table 1. | Demogran | hv of  | children | admitted | with | denoue |
|----------|----------|--------|----------|----------|------|--------|
| Table 1: | Demograd | IIV UI | ciniuren | aummeu   | with | uengue |

of both confirmed (Group A) and clinical dengue (Group B) were compared for any statistically significant differences. Binary logistic regression analysis was done to assess factors associated with increased mortality. Periodical clinical and laboratory problem listing of patients is better than attempting at dengue classification [10]. Hence, these manifestations are listed in detail in this study.

#### RESULTS

Total pediatric admissions at Niloufer Hospital for the year 2015 were 18,203, of which 13,750 were from 01-06-2015 to 30-11-2015. Of these 13750 records, we could trace 282 confirmed dengue cases, 407 clinical dengue cases, 4 confirmed dengue deaths, and 24 clinical dengue deaths making a total of 717 dengue records. CFR, when confirmed and unconfirmed cases were taken together, was 4.06 % (95% confidence interval: 2.56-5.57). Demography, presenting symptoms, signs observed, and results of investigations collected from the case records are presented in Tables 1-6. As some medical records did not have sub-details documented, the numbers of records with documented sub-details were present in the patient, or not available in the record, they were left blank in the tables.

Serology of 282 children of the confirmed group showed 65 had IgM, 45 IgG, 67 NS1, 50 had both IgM and IgG, 29 both IgM and NS1, and 15 had both IgG and NS1 positive results and 11 showed positive results for all the three (IgM, IgG, and NS1) tests. Of the four confirmed deaths, 2 were IgM and NS1 positive, 1 was NS1 positive, and another was IgG positive.

Comparison of proportions of individual clinical details of the total cases between the confirmed and clinical dengue groups yielded no statistically significant differences (p>0.05) in all entries including age group and sex distributions except for rural-urban proportions, diarrhoea, cold, cough, hypotension, decreased urine output, wheezing, decreased platelet count,

| Domographic      | Confirmed asses n (%)   | Unconfirmed cases n (%)   | Confirmed deaths n (%)   | Unconfirmed deaths n (%)  |
|------------------|-------------------------|---------------------------|--------------------------|---------------------------|
| characters       | Commined cases, ii (70) | Oncommined cases, if (70) | Commined deaths, II (70) | Uncomm med deatns, n (70) |
| Total cases      | 282                     | 407                       | 4                        | 24                        |
| Age group        |                         |                           |                          |                           |
| 1 month-1 year   | 43 (15.2)               | 49 (12.4)                 | 2 (50)                   | 10 (41.7)                 |
| 1-5 year         | 87 (30.9)               | 144 (35.4)                | 2 (50)                   | 11 (45.8)                 |
| 6-10 year        | 117 (41.5)              | 165 (40.5)                | 0                        | 3 (12.5)                  |
| 11-15 year       | 35 (12.4)               | 49 (12.4)                 | 0                        | 0                         |
| Sex              |                         |                           |                          |                           |
| Male             | 159 (56.4)              | 225 (55.3)                | 1 (25)                   | 9 (37.5)                  |
| Female           | 123 (43.6)              | 182 (44.7)                | 3 (75)                   | 15 (62.5)                 |
| Residential area |                         |                           |                          |                           |
| Urban            | 117 (41.5)              | 237 (58.2)                | 1 (25)                   | 10 (41.7)                 |
| Semi urban       | 16 (5.67)               | 13 (3.2)                  |                          | 5 (20.8)                  |
| Rural            | 148 (52.5)              | 156 (38.3)                | 3 (75)                   | 8 (33.3)                  |
| Missing data     | 1 (0.35)                | 1 (0.24)                  |                          | 1 (4.2)                   |

| Table 2: | <b>Symptoms</b> | of children | admitted | with dengue |
|----------|-----------------|-------------|----------|-------------|
|          |                 |             |          |             |

| Symptoms                     | Confirmed dengue |                      | Unconfirmed dengue |                       | <b>Confirmed deaths</b> |                    | <b>Unconfirmed deaths</b> |                        |
|------------------------------|------------------|----------------------|--------------------|-----------------------|-------------------------|--------------------|---------------------------|------------------------|
|                              | n (%)            | Mean±SD<br>(range)   | n (%)              | Mean±SD<br>(range)    | n (%)                   | Mean±SD<br>(range) | n (%)                     | Mean±SD<br>(range)     |
| Total cases                  | 282              |                      | 407                |                       | 4                       |                    | 24                        |                        |
| Fever duration (days)        | 282 (100)        | 5.22±2.17 (1-15)     | 399 (98)           | 4.91±2.67 (1-15)      | 4 (100)                 | 3.33 (3-4)         | 21 (87.5)                 | 3.9±3.24 (0.1-15)      |
| Vomiting<br>(frequency/day)  | 163 (57.8)       | 3.41±2.14 (1-10)     | 220 (54)           | 3.88±2.72 (1-20)      | 2 (50)                  | 3 (2-4)            | 11 (45.8)                 | 4.3±2.54 (2-10)        |
| Diarrhoea<br>(frequency/day) | 20 (7.1)         | 4.86±2.5 (2-10)      | 50 (12.3)          | 5.21±2.6 (2-150       | 0                       | -                  | 2 (8.3)                   | 6 (2-10)               |
| Seizures duration            | 17 (6)           | 9.7±8.23<br>(0.5-30) | 28 (6.9)           | 6.66±3.28<br>(0.2-30) | 3 (75)                  | 15 (7.1)           | 14 (58.3)                 | 15.75±18.83<br>(3-600) |
| Generalized                  | 17 (100)         |                      | 27 (96.4)          |                       | 2 (66.6)                |                    | 13 (92.8)                 |                        |
| Partial                      | 0                |                      | 1 (3.6)            |                       | 1 (33.3)                |                    |                           |                        |

#### Table 3: Symptoms of children admitted with dengue

| Symptoms n (%)                | Confirmed dengue | Unconfirmed dengue | <b>Confirmed deaths</b> | Unconfirmed deaths |
|-------------------------------|------------------|--------------------|-------------------------|--------------------|
| Total cases                   | 282              | 407                | 4                       | 24                 |
| Abdominal pain present        | 124 (44)         | 185 (45.4)         |                         |                    |
| Site (data available)         | 73               | 97                 |                         |                    |
| Right upper quadrant          | 48 (65.7)        | 69 (71.1)          |                         |                    |
| Epigastrium                   | 14 (19.2)        | 14 (14.4)          |                         |                    |
| Left upper quadrant           | 1 (1.4)          |                    |                         |                    |
| Periumbilical                 | 7 (9.6)          | 11 (11.3)          |                         |                    |
| Right lower quadrant          | -                | 1 (1)              |                         |                    |
| Right lower and left lower    | 1 (1.4)          | 1 (1)              |                         |                    |
| Epigastrium and periumbilical | 1 (1.4)          | -                  |                         |                    |
| All areas                     | 1 (1.4)          | 1 (1)              |                         |                    |
| Bleeding manifestations       |                  |                    |                         |                    |
| Gum bleed                     | 2 (0.7)          | 1 (0.24)           |                         | 2 (8.3)            |
| Epistaxis                     | 20 (7.1)         | 19 (4.7)           | 1 (25)                  | 1 (4.2)            |
| Malena                        | 79 (28)          | 104 (25.5)         | 2 (50)                  | 5 (20.8)           |
| Hematuria                     | 10 (3.5)         | 11 (2.7)           |                         | 1 (4.2)            |
| Hematemesis                   | 1 (0.3)          | 9 (2.2)            |                         | 1 (4.2)            |
| Rash                          | 79 (28)          | 91 (22.4)          |                         | 1 (4.2)            |
| Ecchymosis                    | 3 (1)            | 3 (0.74)           |                         | 1 (4.2)            |
| Itching                       | 9 (3.2)          | 17 (4.2)           |                         |                    |
| Respiratory distress          | 11 (3.9)         | 23 (5.6)           | 1 (25)                  | 5 (20.8)           |
| Altered sensorium             | 3 (1)            | 4 (1)              | 3 (75)                  | 13 (54.2)          |
| Giddiness                     | 3 (1)            | 6 (1.5)            |                         |                    |
| Jaundice                      | 3 (1)            | 1 (0.25)           |                         |                    |
| Headache                      | 42 (14.9)        | 76 (18.7)          |                         |                    |
| Cold                          | 30 (10.6)        | 82 (20.1)          |                         | 6 (25)             |
| Cough                         | 47 (16.7)        | 115 (28.2)         |                         | 9 (37.5)           |
| Excessive cry                 | 5 (1.8)          | 8 (2)              |                         |                    |
| Swelling                      | 16 (6)           | 34 (8.3)           |                         | 1 (4.2)            |
| Decreased urine output        | 15 (5.7)         | 14 (3.4)           |                         | 3 (12.5)           |
| Burning micturition           | 2 (0.7)          | 12 (3)             |                         | 1 (4.2)            |
| Myalgia                       | 49 (17.4)        | 75 (18.4)          |                         |                    |
| Joint pain                    | 7 (2.5)          | 12 (3)             |                         |                    |
| Eye pain                      | 2 (0.7)          | 3 (0.74)           |                         |                    |

#### Table 4: Signs noticed in children admitted with dengue

| Signs, n (%)                    | Confirmed dengue | Unconfirmed dengue | <b>Confirmed deaths</b> | Unconfirmed deaths |
|---------------------------------|------------------|--------------------|-------------------------|--------------------|
| Total cases                     | 282              | 407                | 4                       | 24                 |
| Skin rash                       | 158 (56)         | 218 (53.6)         |                         | 8 (33.3)           |
| Flushing                        | 144 (91.1)       | 193 (88.5)         |                         | 8 (33.3)           |
| Petechial spots                 | 7 (4.4)          | 9 (4.1)            |                         |                    |
| Flushing and petechial spots    | 5 (3.2)          | 7 (3.2)            |                         |                    |
| Erythematous popular rash       | 0                | 7 (3.21)           |                         |                    |
| Missing detail                  | 2 (1.3)          | 2 (0.92)           |                         |                    |
| Congested Conjunctiva           | 16 (5.7)         | 33 (8.1)           |                         | 2 (8.3)            |
| Sub-conjunctival hemorrhage     | 1 (0.35)         | 1 (0.25)           |                         |                    |
| Pallor                          | 10 (3.5)         | 25 (6.1)           | 2 (50)                  | 4 (16.7)           |
| Icterus                         | 3 (1)            | 4 (1)              |                         | 1 (4.2)            |
| Edema                           | 55 (19.5)        | 67 (16.5)          | 2 (50)                  | 6 (25)             |
| Cool peripheries                | 20 (7.1)         | 38 (9.3)           | 1 (25)                  | 12 (50)            |
| Prolonged capillary refill time | 12 (4.25)        | 11 (2.7)           | 1 (25)                  | 5 (20.8)           |
| Elevated JVP                    | 3 (1)            | 7 (1.7)            |                         |                    |
| Bradycardia                     | 13 (4.6)         | 18 (4.4)           |                         | 8 (33.3)           |
| Decreased urine output          | 25 (8.9)         | 15 (3.7)           |                         | 1 (4.2)            |
| Respiratory distress            | 3 (1)            | 14 (3.4)           | 3 (75)                  | 6 (25)             |
| Wheezing                        | 5 (1.8)          | 34 (8.3)           | 2 (50)                  | 6 (25)             |
| Crepitations                    | 4 (1.4)          | 14 (3.4)           | 2 (50)                  | 7 (29.2)           |
| Stridor                         | -                | 1 (0.25)           | -                       | 1 (4.2)            |
| Hepatomegaly                    | 198 (70.2)       | 276 (67.8)         | 2 (50)                  | 19 (79.2)          |
| Tender Hepatomegaly             | 123 (62.1)       | 160 (58)           | 1 (50)                  | 2 (10.5)           |
| Dehydration                     | 1 (0.35)         | 7 (1.7)            | 1 (25)                  | 4 (16.7)           |
| Some                            | 1 (100)          | 6 (85.7)           | 1 (25)                  | 3 (75)             |
| Severe                          | 0                | 1 (14.3)           |                         | 1 (25)             |
| Spleenomegaly                   | 16 (5.7)         | 24 (5.9)           |                         | 2 (8.3)            |
| Muscle tenderness               | 12 (4.25)        | 8 (2)              |                         |                    |
| Altered sensorium               | 2 (0.7)          | 1 (0.25)           | 4 (100)                 | 14 (58.3)          |
| Meningeal signs                 | 0                | 0                  |                         | 3 (12.5)           |

#### Table 5: BP details noticed in children admitted with dengue

| BP                          | Confirmed dengue |                        | Unconfirmed dengue |                         | <b>Confirmed deaths</b> |                    | Unconfirmed deaths |                   |
|-----------------------------|------------------|------------------------|--------------------|-------------------------|-------------------------|--------------------|--------------------|-------------------|
|                             | n (%)            | Mean±SD<br>(range)     | n (%)              | Mean±SD<br>(range)      | n (%)                   | Mean±SD<br>(range) | n (%)              | Mean±SD (range)   |
| Total cases                 | 282              |                        | 407                |                         | 4                       |                    | 24                 |                   |
| Hypotension (duration in h) | 181 (64.2)       | 44.21±31.28<br>(1-144) | 204 (50.1)         | 47.13±40.4<br>(0.5-264) | 2 (50)                  | 39 (6-72)          | 14 (58.3)          | 18.5±15.35 (5-42) |
| Systolic BP<70 mmHg         | 25 (13.8)        |                        | 26 (12.7)          |                         | 1 (25)                  |                    | 6 (25)             |                   |
| Systolic BP>70 mmHg         | 154 (85.1)       |                        | 176 (86.3)         |                         | 1 (25)                  |                    | 4 (16.7)           |                   |
| Hypertension                | 1 (0.35)         |                        | 1 (0.25)           |                         |                         |                    | 1 (4.2)            |                   |

**BP: Blood pressure** 

and hyperchloremia (p < 0.05). These differences stemmed from unintentional grouping of milder dengue into unconfirmed group as less severe cases were less investigated. The proportions of the findings in death groups could not be compared as the sample size was small.

Serology kits using IgM immunochromatography tested at the institute have low sensitivity of 36.2% (156 positives of 430 cases tested), falling in the lower range of 20.5-97.7% sensitivity of similar kits [7]. Sensitivity of the NS1 RDT kits was 80.6% (125 positives of 155 cases tested). Clinical and other laboratory details were similar between both the groups for nearly 90% of the symptoms, signs, and investigations. This necessitates the understanding by the clinicians of the superiority of clinical diagnostic skills over laboratory reliance for confirmation.

Logistic regression test was done to explore the predictors of mortality in these patients and results are shown in Table 7. Hosmer and Lemeshow goodness-of-fit test resulted in Chi-square

| Investigations, positive/available results (%) | <b>Confirmed cases</b> | Unconfirmed cases | <b>Confirmed deaths</b> | Unconfirmed deaths |
|--|------------------------|-------------------|-------------------------|--------------------|
| Total cases                                    | 282                    | 407               | 4                       | 24                 |
| Thrombocytopenia (<1,00,000/µL)                | 225/277 (81.23)        | 233/370 (63)      | 2/3 (66.7)              | 8/13 (61.5)        |
| Leukopenia (<4000/µL)                          | 52/277 (18.77)         | 57/370 (15.4)     | 0                       | 0                  |
| High PCV (>20%)                                | 51/161 (31.68)         | 81/192 (42.19)    | 1/1 (100)               | 2/2 (100)          |
| Elevated APTT                                  | 3/4 (75)               | 3/5 (60)          | 1/1 (100)               |                    |
| INR>1.3  | 34/40 (85)             | 51/62 (82.2)      | 3/3 (100)               | 4/6 (66.7)         |
| Proteinuria                                    | 15                     | 38                |                         | 1                  |
| Elevated bilirubin                             | 5/41 (12.2)            | 8/63 (12.7)       | 1/2 (50)                | 2/3 (66.6)         |
| Elevated AST                                   | 6/7 (85.7)             | 2/5 (40)          | 1/1 (100)               | 2/2 (100)          |
| Elevated ALT                                   | 12/17 (70.6)           | 16/35 (45.7)      |                         | 2/2 (100)          |
| Hypoalbuminemia                                | 3/20 (15)              | 2/30 (6.7)        |                         |                    |
| Elevated creatinine                            | 3/101 (3)              | 3/149 (4.5)       |                         | 1/7 (14.3)         |
| Elevated blood urea                            | 10/103 (9.7)           | 7/150 (4.7)       |                         | 3/9 (33.3)         |
| Hyponatremia                                   | 10/99 (10.1)           | 8/146 (5.5)       |                         |                    |
| Hypernatremia                                  | 1/99 (1)               | 2/146 (1.4)       |                         | 1/9 (11.1)         |
| Hypokalemia                                    | 4/99 (4)               | 12/147 (8.2)      |                         |                    |
| Hyperkalemia                                   | 2/99 (2)               | 4/147 (2.7)       |                         |                    |
| Hyperchloremia                                 | 20/49 (40.8)           | 10/63 (15.9)      |                         | 4/8 (50)           |
| Hypocalcemia                                   | 3/11 (27.3)            | 1/12 (8.3)        |                         |                    |
| Hypoglycemia                                   | 2/41 (4.9)             | 0                 |                         |                    |
| Hyperglycemia                                  | 2/41 (4.9)             | 3/49 (6.1)        |                         | 2/5 (40)           |

AST: Aspartate aminotransferase, ALT: Alanine transaminase, PCV: Packed cell volume

| <b>Table 7: Binary</b> | logistic | regression | analysis | of risk ( | of mortality | ' in | dengue |
|------------------------|----------|------------|----------|-----------|--------------|------|--------|
|------------------------|----------|------------|----------|-----------|--------------|------|--------|

| Variable             | Standard error of coefficient | p value Odds ratio |         | 95% confidence interval |          |
|----------------------|-------------------------------|--------------------|---------|-------------------------|----------|
|                      |                               |                    |         | Lower                   | Upper    |
| Age<5 years          | 0.878                         | 0.008              | 10.108  | 1.808                   | 56.510   |
| Female sex           | 0.684                         | 0.255              | 2.179   | 0.570                   | 8.327    |
| Bleeding             | 0.749                         | 0.443              | 0.563   | 0.130                   | 2.444    |
| Seizures             | 0.798                         | 0.047              | 4.892   | 1.024                   | 23.361   |
| Altered sensorium    | 1.022                         | 0.000              | 266.218 | 35.932                  | 1972.364 |
| Bradycardia          | 0.811                         | 0.000              | 36.551  | 7.452                   | 179.278  |
| Respiratory distress | 0.951                         | 0.096              | 4.862   | 0.755                   | 31.331   |
| Hypotension          | 0.791                         | 0.887              | 1.119   | 0.237                   | 5.276    |
| Systolic BP<70 mmHg  | 0.996                         | 0.020              | 10.085  | 1.433                   | 70.979   |

**BP: Blood pressure** 

of 7.792 and a nonsignificant difference between observed and estimated outcomes (p=0.454). As p>0.05, this model passes the test. Age <5 years, seizures, altered sensorium, bradycardia, and systolic blood pressure <70 mmHg were significantly associated with increased mortality in dengue.

#### DISCUSSION

Age distribution of affected children shows that in infancy, 6-9 months age group, the period of waning passive immunity, is the peak period of dengue affection. There were less cases in the 1-1.5 year age group, and after this age, there was a small rise in the incidence. This is in concordance with previous studies. Infants born to dengue-immune mothers had higher risk of severe disease, even though it was their first infection [11,12]. Nearly 90% of dengue deaths occurred in children aged <5 years emphasizing that this age group needs high priority care. CFR in girls was 5.9% (95% CI: 3.17-8.63), and in boys, it was 2.6% (95% CI: 0.99-4.22), however, the difference was not significant. There is evidence in literature that female sex predisposes to severe dengue [13]. Rural areas were no less affected than urban areas due to adaptation of urban lifestyle, pointing to the need for training and strengthening primary care and proper referral system.

Presenting symptoms with >5% frequency in the decreasing order were fever, vomiting, abdominal pain, malena, skin rash, cough, myalgia, headache, cold, diarrhea, swelling of body, epistaxis, seizures, decreased urine, and respiratory distress. Few infants with tender hepatomegaly presented with excessive cry due to sudden liver enlargement. Seizures (27% died, p=0.047) and altered sensorium (70% died, p=0.000) were associated with increased mortality mostly in under five age group (p=0.008). Majority of the children complained of pain in right hypochondrium (66-71%) followed by epigastrium (14-19%) pointing to liver enlargement and gastritis. In children <5 years (especially infants), who presented with respiratory infections resembling bronchiolitis and gastroenteritis, hepatomegaly and flushing served as differentiating findings.

Observed signs with >5% frequency in decreasing order were hepatomegaly, hypotension, rash, edema, cool peripheries, conjunctival congestion, decreased urine output, wheezing, splenomegaly and pallor. Isolated symptom or sign presentations of dengue are also seen during epidemics. Cool peripheries, prolonged CRT, pallor, elevated jugular venous pressure (JVP), and wheezing were less documented in the case records, though their observed frequencies at bedside were much higher than the presented results. Nearly one-third of patients had elevation of JVP persisting for 24-48 h indicating transient myocardial dysfunction.

A large body of clinical and experimental evidence points to the involvement of liver in pathobiology of dengue infections. The hepatocytes are directly involved in infection as a site of dengue replication, possibly adding to the total viral burden [14]. Nearly 70% had hepatomegaly, 60% of the enlarged livers were tender in this study. Similar evidence states that liver is palpably enlarged in up to 75% of patients, with variable splenomegaly [15]. Tender hepatomegaly has few differential diagnoses and can be used to diagnose PD. Tender hepatomegaly is rare in malaria [16]. Hepatomegaly is usually observed in enteric fever after the first week of illness in contrast to dengue, and only 12% of enlarged livers were tender in complicated multi-drug resistant enteric fever. Hepatomegaly is 2-3 times less common in paratyphoid fever than enteric fever [17]. Tender liver in viral hepatitis and liver abscess is not associated with early shock or rash. Tender liver in congestive cardiac failure presents with abnormal cardiac examination findings. Budd-chiari syndrome presents with localized findings associated with tender hepatomegaly.

Liver enlargement in dengue posed a problem of appreciation because of its soft consistency, especially in under five age group. This can be overcome using the method of pressing the middle finger tangential to the abdominal surface checking for differential resistance in all the quadrants of the abdomen. It was observed by the authors at bedside that, using this method, we get hepatomegaly frequency near to 100% in PD. Tenderness is influenced by the day on which patient is examined after hepatomegaly had set in. Tenderness usually decreased after 3 days of presentation.

Blanchable flushing of the skin with centrifugal distribution, predominantly affecting hands and feet was the commonest pattern of rash. Truncal, neck, and facial flushing were less commonly noticed, probably due to skin color of the children. The lateral border of the sole was the consistent site of noticeable flushing. Flushing becomes more prominent when feet are in dependent position. As many Indian children have pallor, appreciation of flushing requires expertise. High yielding laboratory results in the decreasing order of frequency were INR >1.3, thrombocytopenia, elevated APTT, increased packed cell volume >20%, hyperchloremia and leukopenia. Common findings in ECG were bradycardia and low voltage QRS complexes. Common findings on USG were hepatomegaly, gall bladder wall edema, and free fluid in peritoneal cavity, pleural effusion and splenomegaly. Chest radiographs showed hyperinflation as the most frequent finding followed by effusions, and perihilar nonhomogenous opacities. Abdominal radiography had shown hepatomegaly sometimes reaching up to right iliac fossa in nearly 100% patients. A combination of hyperinflation and hepatomegaly on radiograph has very few differential diagnoses; hence, can be used in the epidemic scenario as a definite feature of PD where skilled ultrasonography reporting is not available.

Comparison of the results of Groups A and B shows that clinical diagnosis is as good as having confirmation. This infers that treating patients with fluids according to dengue protocol and other supportive measures need not wait for confirmation. Confirmatory laboratory studies serve the purpose of confirmation of epidemics. Unfortunately, an ideal diagnostic test that permits early and rapid diagnosis, is affordable for different health systems, is easy to perform, and has a robust performance, is not yet available [1]. Except rapid tests, all other methods require 1 day to 2 weeks' time and are of no use for case management as time to death is narrow once patient is in deterioration. Similar guidelines regarding acting on suspicion without waiting for confirmation were issued for rickettsial infections by Centers for Disease Control and Prevention [18].

The differential diagnosis of dengue includes rickettsial infections and relapsing fever. Filoviruses, yellow fever virus, bunyaviruses, and arenaviruses can cause increased vascular permeability and acute shock, and their treatment is supportive as it is in dengue. Clinicians who consistently look for the features listed above can get familiarized with the way to diagnose dengue in no time and serve the patient in the hour of need.

#### CONCLUSIONS

These data support that clinical diagnosis is as good as having confirmation of dengue. Clinical diagnosis in light of the epidemiology using right hypochondrium pain, malena, tender hepatomegaly, centrifugal blanchable flushing, and hypotension as definite pointers of dengue avoids vagueness. Rapid tests are not mandatory, and other laboratory methods cannot serve in the hour of need. Laboratory confirmation serves epidemiological purposes. Supportive treatment, timely escalation of fluid therapy for clinical dengue is more essential than confirmation. Further studies should include clinical dengue reporting to avoid under-reporting.

#### REFERENCES

<sup>1.</sup> World Health Organization. Dengue: Guidelines for Diagnosis, Treatment Prevention and Control, New Edition. Geneva: WHO; 2009.

## Srigade and Bingi

- Gupta N, Srivastava S, Jain A, Chaturvedi UC. Dengue in India. Indian J Med Res. 2012;136(3):373-90.
- Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7.
- CDC.gov. Atlanta: Dengue Laboratory Guidance and Diagnostic Testing; 2016 Jan 20. Available from: http://www.cdc.gov/dengue/clinicallab/ laboratory.html. [Last cited on 2016 Oct 24].
- Hermann LL, Thaisomboonsuk B, Poolpanichupatam Y, Jarman RG, Kalayanarooj S, Nisalak A, et al. Evaluation of a dengue NS1 antigen detection assay sensitivity and specificity for the diagnosis of acute dengue virus infection. PLoS Negl Trop Dis. 2014;8(10):e3193.
- Chaterji S, Allen JC Jr, Chow A, Leo YS, Ooi EE. Evaluation of the NS1 rapid test and the WHO dengue classification schemes for use as bedside diagnosis of acute dengue fever in adults. Am J Trop Med Hyg. 2011;84(2):224-8.
- Hunsperger EA, Yoksan S, Buchy P, Nguyen VC, Sekaran SD, Enria DA, et al. Evaluation of commercially available anti-dengue virus immunoglobulin M tests. Emerg Infect Dis. 2009;15(3):436-40.
- Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: An integrated view. Clin Microbiol Rev. 2009;22(4):564-81.
- 9. Kularatne SA. Dengue fever. BMJ. 2015;351:h4661.
- Srikiatkhachorn A, Rothman AL, Gibbons RV, Sittisombut N, Malasit P, Ennis FA, et al. Dengue--how best to classify it. Clin Infect Dis. 2011;53(6):563-7.
- Kliks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. Am J Trop Med Hyg. 1988;38(2):411-9.

- Halstead SB, Lan NT, Myint TT, Shwe TN, Nisalak A, Kalyanarooj S, et al. Dengue hemorrhagic fever in infants: research opportunities ignored. Emerg Infect Dis. 2002;8(12):1474-9.
- Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: A continuing global threat. Nat Rev Microbiol. 2010;8 12 Suppl: S7-16.
- Smith DR, Khakpoor A. Involvement of the liver in dengue infections. Dengue Bull. 2009;33:75-86.
- Vaughn DW, Barrett A, Flaviviruses TS. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennet's Principles and Practice of Infectious Diseases. 7<sup>th</sup> ed. Philadelphia, PA, USA: Churchill Livingstone Elsevier; 2010. p. 2145.
- Sowunmi A. Hepatomegaly in acute falciparum malaria in children. Trans R Soc Trop Med Hyg. 1996;90(5):540-2.
- Jagadish K, Patwari AK, Sarin SK, Prakash C, Srivastava DK, Anand VK. Hepatic manifestations in typhoid fever. Indian Pediatr. 1994;31(7):807-11.
- McQuiston J. Infectious diseases related to travel rickettsial (spotted & typhus fevers) & related infections (anaplasmosis & ehrlichiosis). CDC Health Information for International Travel. Ch. 3. Geneva: CDC; 2016.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Srigade V, Bingi K. Dengue - should we look for confirmation? Indian J Child Health. 2017; 4(1):91-97.