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Comparison of presentation, clinical course and outcomes of dengue among infants and older children in India

B.K. Bhakhri[1], V. Tyagi[1], R. Prajapati[1], D.K. Singh[1], R. Rai[2], N. Singh[1]

[1]Department of Pediatrics, Post Graduate Institute of Child Health, NOIDA, Sector 30, Uttar Pradesh, India
[2]Department of Neonatology and MRH, Post Graduate Institute of Child Health, NOIDA, Sector 30, Uttar Pradesh, India

ABSTRACT:

— ***Objective:*** There is limited literature regarding the clinical symptoms and laboratory parameters in infants with dengue infection, especially from north India. We aim to study the symptomatology, laboratory findings and clinical outcomes of dengue infection in infants.

— ***Patients and Methods:*** Records of 802 children admitted with dengue infection, based on NS-1 antigen and/or IgM ELISA testing, were collected. Among these, 51 children belonged to the infant (0-12 months) age group. Clinical characteristics, hematological parameters and clinical outcomes were compared between infant and non-infant groups.

— ***Results:*** A significantly higher proportion of infants with dengue fever had loose stool (35.3% *vs.* 3%), cough (31.4% *vs.* 1.7%) and seizure (17.6% *vs.* 1%) at presentation. Severe thrombocytopenia (35.2% *vs.* 57%) and platelet transfusion requirement (13.7% *vs.* 27%) was significantly lower in the infant group. The hemoglobin concentration [g%, mean (SD)] at presentation was significantly lower among infants [10.7 (2.25) *vs.* 11.8 (2.3)]. A significantly lower hematocrit (%) [34.5 (6.63) *vs.* 39.1 (7.18)] was recorded at presentation in infants. Mean platelet volume (fL) was significantly lower among infants in our study [10.4 (3.1) *vs.* 11.3 (2.49)]. Among liver function parameters, serum albumin (g/dL) level was significantly lower in older children [4.0 (0.72)], compared to infants [4.3 (0.68)].

— ***Conclusions:*** Our study findings suggest that infant dengue infection can present like any other acute viral illness. Also, infants have an overall milder course of illness due to dengue infection, compared to older children.

— ***Keywords:*** *Dengue, Infants, Severity, Clinical outcome, India.*

INTRODUCTION

Dengue is a viral infection caused by Dengue virus (DENV), belonging to the *Flaviviridae* family. There are four closely related, but antigenically distinct serotypes of the virus (DENV 1-4). The virus is spread to humans by the bite of the infected mosquito *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*. According to WHO[1], 50% of the world population lives in dengue-endemic regions, with up to 70% of the actual disease burden reported from Asia. In the last 2 decades, there has been an eight-fold increase in cases reported to the WHO. Dengue cases and deaths seemingly declined in 2020-2021, but it could be attributed to inadequate case reporting during the COVID-19 pandemic[2].

India recorded 0.12 million cases in 2021 (until October), with 90 dengue deaths[3]. Although all age groups are susceptible to infection, the maximum incidence

Corresponding Author: N. Singh, MD; e-mail: nupursingh0701@gmail.com

among children has been reported[4] in the age group of 5-15 years. Murhekar et al[5] reported 28.4% positivity among the samples from clinically suspected dengue infection in India. The positivity varied from 7.7% to 37%, reaching its maximum in the months of September and October. The overall dengue seroprevalence in India is reported as 48.7%, distributed heterogeneously across the different regions and showing a gradual rise from childhood to elderly age groups[6,7]. The pooled case fatality ratio estimated in a systematic review was reported as 2.6% (95% CI, 2-3.4%). Significant outbreaks have been observed to be happening more frequently over the last 3 decades in India. All four dengue virus serotypes have been reported[8] in circulation in the endemic areas. The predominant serotype may vary depending on the region and year of the outbreak. The economic burden of dengue in India, $ 1.51 billion reported in the year 2013, was observed[9] to be expanding almost four-fold in the next 3 years, possibly due to the increasing incidence and better reporting of cases.

Dengue infection can present as an asymptomatic illness (most common), undifferentiated fever or severe illness (with shock/hemorrhage). In adults and older children, severe forms of dengue infection have been strongly associated with the occurrence of secondary infection with a heterotypic virus. In regions with high endemicity, infants born to dengue-infected mothers can also present with severe forms of illness during primary infection. This occurs due to antibody enhancement caused by the transplacental transfer of IgG antibodies from previously infected mothers. Dengue virus infection can have a varied clinical spectrum, ranging from asymptomatic infection (up to 80%), undifferentiated fever to severe dengue (dengue hemorrhagic fever and shock)[10]. Studies[11] have reported a higher proportion of symptomatic dengue infection and severe presentation among infants. In endemic regions, maternally-derived anti-dengue IgG antibodies have been implicated in causing severe illness in infants[12]. These antibodies are found in high titers (corresponding to maternal antibody levels) up to 4 months of life. After this period, a decline in antibody titers to sub-protective levels has been shown[11], putting infants at risk for antibody-dependent enhancement, leading to manifestations of severe dengue infection[13]. Studies[14-16] have also reported that the risk of severe infection peaks from 7 to 9 months of age.

A study[17] from Puducherry, in India, reported that dengue in infants contributed 2.7% of the total pediatric load, with no case of severe dengue in this age group. Similarly, another study[18] on pediatric dengue from Odisha, in India, did not report any case of severe dengue in infants. On the other hand, a study conducted in Vellore, in India, had a higher proportion of infants (25%) among under-18 children admitted with dengue fever. Of these, 53% of infants had severe illness[14]. According to another study[19] performed in Chennai, India, infants constituted 20% of the total pediatric cases. Severe infection was seen in 17% of these infants. Studies[20,21] from other Asian countries have reported a lower incidence of dengue infection in infants. Limited data is available regarding the clinical features and laboratory findings in infants infected with dengue, especially from northern India. With this study, we aimed to study the clinical features, laboratory parameters and clinical outcomes of dengue infection in infants, in comparison with older children.

PATIENTS AND METHODS

A retrospective observational analytical study was conducted at a pediatric tertiary care hospital in north India. The Ethics Committee of the Postgraduate Institute of Child Health, Noida, UP, provided approval for the conduct of the study while waiving the consent for retrospectively collected anonymized data (PGICH-IEC-2022-05-IM-02, dated 07/05/2022). Data were collected from the records of the patients who had been admitted with laboratory-confirmed dengue infection (acute febrile illness with NS1 antigen and/or IgM antibody positive) between 1st June 2016 and 31st December 2021. Patients with warning signs and severe illness (based on WHO classification[22]) are admitted for in-patient management as per departmental policy. Apart from these, children admitted with symptoms like febrile seizure, cough with fast breathing, and high purge rate, who tested positive for dengue, were also included in the study.

Patients were divided into 2 groups based on their age, infants (0 - <12 months age) and non-infants (12 months - 18 years). The following data were recorded: demographic details (age, gender), clinical characteristics (duration of symptoms, presence of fever, vomiting, loose stools, hemorrhagic manifestations which include petechiae, epistaxis, menorrhagia, melena, hematuria, clinical jaundice, cough, tachypnea, seizure, hepatomegaly, and splenomegaly). The initial laboratory parameters at the time of hospital admission recorded were: complete blood counts, red cell indices, hematocrit, mean platelet volume, and liver function test. Tests were repeated later as per clinical requirements. The minimum platelet count during the hospital stay was also recorded. Outcome measures included: the duration of hospital stay, the requirement of blood component transfusion, the requirement of inotrope support, and mortality. Development of complications like acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), pericardial effusion, disseminated intravascular coagulation (DIC), and encephalopathy, were also noted.

The diagnosis of dengue fever was based on NS-1 antigen (Biorad PlateliaTM Dengue NS1 Antigen, Biorad Laboratories, Marnes-La-Coquette, France) and/or IgM ELISA (Panbio Dengue IgM Capture ELISA, Panbio Kit, Alere, Waltham, MA, USA) antibody detection. For children presenting within the first 3 days of illness, NS1 antigen testing alone was performed. For those who presented beyond day 5, only IgM antibody was tested. For those presenting between days 3 and 5, or where the exact duration was not clear, both antigen and antibody testings were done. The illnesses were managed as per

the latest standard protocols proposed by WHO[22]. Standard departmental protocol-based criteria were used for blood component transfusion. The packed red cell was transfused to hemodynamically unstable children with hemoglobin concentration <10 gm%, whereas stable children were transfused at hemoglobin <8 gm%. Platelet concentrate was transfused in children with mucosal bleed and platelet count <20,000/cm^3 or at count <10,000/ cm^3, irrespective of bleeding.

Statistical Analysis

Data entry into an Excel sheet was cross-checked by two reviewers. For analysis and graphical representation, the IBM SPSS statistical software version 25.0 (IBM Corp., Armonk, NY, USA) was used. Descriptive statistics were used for the representation of data (frequency, mean and SD, median and IQR). The two groups were compared using Chi-square or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Statistical significance was considered at a *p*-value <0.05.

RESULTS

A total of 1,485 children (<18 years) tested positive for dengue infection during this period, and among them, 802 were admitted. 30% of children tested positive for NS1 antigen, 42% were positive for IgM antibody, whereas 28% of children tested positive for both. A comparison of baseline characteristics and clinical outcomes between infants and non-infants is presented in Table 1. Of the total cases, 51 (6%) children belonged to the infant age group. There was no case of neonatal (<28 days) dengue infection. The mean age (SD) of infants was 6.4 (0) months, with 28 (55%) males. The mean age (SD) in the non-infant group was 8 (4.26) years, with 465 (62%) males. The mean (SD) duration of symptoms at the time of admission was 4.0 (2.63) days in the infant group and 4.7 (1.96) in the non-infant group. The mean (SD) duration of hospitalization was 5.8 (2.38) days in the infant group and 5.3 (1.8) days in the non-infant group. Severe dengue infection was present in a significantly higher proportion of older children (15%) compared to infants (2%). The rest was admitted with variable warning signs. A significantly higher proportion of infants with dengue fever had loose stool, cough, and seizure at presentation. Bleeding manifestations were seen in 10 (19.6%) infants, of which 3 had petechiae, 6 had petechiae with rectal mucosal bleeding, and one had hematuria. On the other hand, 213 (28.3%) older children had some form of bleeding which included petechiae, epistaxis, menorrhagia and hematuria, which were present in 123, 40, 22, and 7 children, respectively. The remaining had both skin and mucosal bleeding. The platelet transfusion requirement was significantly higher in the non-infant group. Inotrope support was required in one (2%) infant compared to 30 (4%) children in the non-infant group. Complications were seen in 49 (6.5%) of the older children, which included acute kidney injury (45%), acute respiratory distress syndrome (25%), disseminated intravascular coagulation (14%),

Table 1. Comparison of baseline characteristics and clinical outcome between infants and non-infants.

Parameter	Infants (N=51)	Non-infants (N=751)	*p*-value
Males	28 (55%)	465 (62%)	>0.05
WHO Case classification			
Severe Dengue	1 (2%)	113 (15%)	**<0.05***
Dengue with warning signs	50 (98%)	638 (85%)	
Fever at presentation	47 (92%)	735 (98%)	**<0.05***
Loose stool	18 (35.3%)	22 (3%)	**<0.05***
Vomiting	16 (31.4%)	424 (56.4%)	**<0.05***
Cough	16 (31.4%)	13 (1.7%)	**<0.05***
Tachypnea at admission	12 (23.5%)	7 (1%)	**<0.05***
Seizure	9 (17.6%)	8 (1%)	**<0.05***
Bleeding manifestation	10 (19.6%)	213 (28.3%)	>0.05
Jaundice	1 (2%)	14 (2%)	>0.05
Hepatomegaly/splenomegaly	15 (29.4%)	238 (31.7%)	>0.05
Complications	1 (2%)	49 (6.5%)	>0.05
Platelet transfusion	7 (13.7%)	202 (27%)	**<0.05***
PRBC transfusion	3 (6%)	32 (4.3%)	>0.05
Inotrope support	1 (2%)	30 (4%)	>0.05
Total duration of symptoms (days)	6.3 (3.0)	7.2 (1.96)	**<0.05***
Total duration of hospitalization (days)	5.8 (2.38)	5.3 (1.8)	**<0.05**
Mortality	0	22 (3%)	>0.05

All values represented in number (%). * *p*-value < 0.01.

Table 2. Comparison of laboratory parameters between infants and non-infants.

Parameter	Infants (N=51)	Non-infants (N=751)	*p*-value
Hemoglobin (g%)	10.7 (2.25)	11.8 (2.3)	**<0.05***
Total leucocyte count (cells/mm³)	11,600 (8,050; 14,650)	5,530 (3,640; 8,745)	-
Platelet count at admission (lac/mm³) *	1.6 (0.54, 2.33)	0.61 (0.34, 1.18)	-
Platelet count (minimum) (lac/mm³)*	0.95 (0.3, 2.0)	0.41 (0.24, 0.7)	-
Severe thrombocytopenia (<50,000/cm³)	18 (35.2%)	427 (57%)	**<0.05***
MCV (fL)	74.4 (12.28)	78.39 (9.71)	**<0.05***
MPV (fL)	10.4 (3.1)	11.3 (2.49)	**<0.05**
RDW (%)	15.1 (2.13)	14.3 (1.61)	**<0.05***
HCT (%)	34.5 (6.63)	39.1 (7.18)	**<0.05***
AST (IU/L) *	129 (59, 295)	158 (76, 306.5)	-
ALP (IU/L) *	68 (38, 104)	90 (45, 191)	-
S. Bilirubin (mg/dL)	0.9 (0.84)	0.8 (0.48)	>0.05
Total protein (g/dL)	6.1 (0.81)	6.5 (2.45)	>0.05
Serum albumin (g/dL)	4.3 (0.68)	4.0 (0.72)	**<0.05***

*= expressed as median (IQR), other values represented in mean (SD). **p*-value < 0.01.

encephalopathy (8%), pericardial effusion (6%). One (2%) child in this group had encephalopathy with myocarditis. Among infants, there was one case complicated by acute kidney injury. There was no mortality among infants, whereas 22 (3%) children succumbed to illness in the non-infant group.

A comparison of laboratory parameters between infants and non-infants is presented in Table 2. Severe thrombocytopenia (<50,000/mm³) was significantly higher in the non-infant group. Infants had significantly lower mean platelet volumes at presentation. The initial hematocrit values were higher in older children. Among liver function parameters, serum albumin (g/dL) level was significantly lower in older children compared to infants. The comparison of total leucocyte count (TLC), platelet count, minimum platelet count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels among infants and non-infants is presented as box and whisker plots in Figure 1.

DISCUSSION

In our study, 51 infants were admitted with dengue fever, which comprised 6% of the total pediatric dengue cases between June 2016 and December 2021. One infant was admitted with severe dengue (shock with AKI), and there was no mortality in this age group.

Although fever was present in the majority of children at presentation, it was seen in a significantly higher proportion of non-infants. Loose stools and respiratory symptoms like cough and tachypnea were found in a significantly higher proportion of infants. The seizure was also more commonly present in infants compared to older children. On the other hand, vomiting was a more frequent presentation in older children. Respiratory symptoms and seizures were uncommon manifestations in this age group. Our findings in infant dengue have been corroborated by previous studies[14,23,24] as well. Other Indian studies[14,19,25] have reported a higher proportion of severe dengue in infants, ranging from 9% from Delhi[25], to 17% from Chennai[19], to 53% from Vellore[14]. In contrast, there was only one case of severe dengue in our study. A similar observation was also made in a study from Thailand[26].

The hemoglobin concentration at presentation was significantly lower among infants. Significantly higher total leucocyte count and lower hematocrit were recorded at presentation in the infant group. Similar findings were seen in the study from Thailand[26]. In our study, the initial platelet count was significantly lower in the non-infant group. Also, a larger proportion of older children had severe thrombocytopenia. Few studies[14,19] have reported the more frequent occurrence of severe thrombocytopenia in infants. However, despite low platelet counts, none of these studies recorded a higher proportion of hemorrhagic manifestation among infants, similar to our findings. Mean platelet volume was significantly lower among infants in our study.

However, comparison of these hematological parameters should be made with caution, keeping in mind age-appropriate reference values for healthy infants and older children. Total leucocyte counts are higher in infants compared to toddlers and older children[27]. The mean platelet count is significantly higher in infants compared to older children. Similarly, mean platelet volume is significantly lower in infants[28].

Strengths and Limitations

Our study has a few important strengths. We describe the clinical presentation, hematological parameters and outcome in many infants. Comparison with older children provides a better understanding of the illness in the infant age group. However, the retrospective nature of the study is a major drawback. Also, a sizable num-

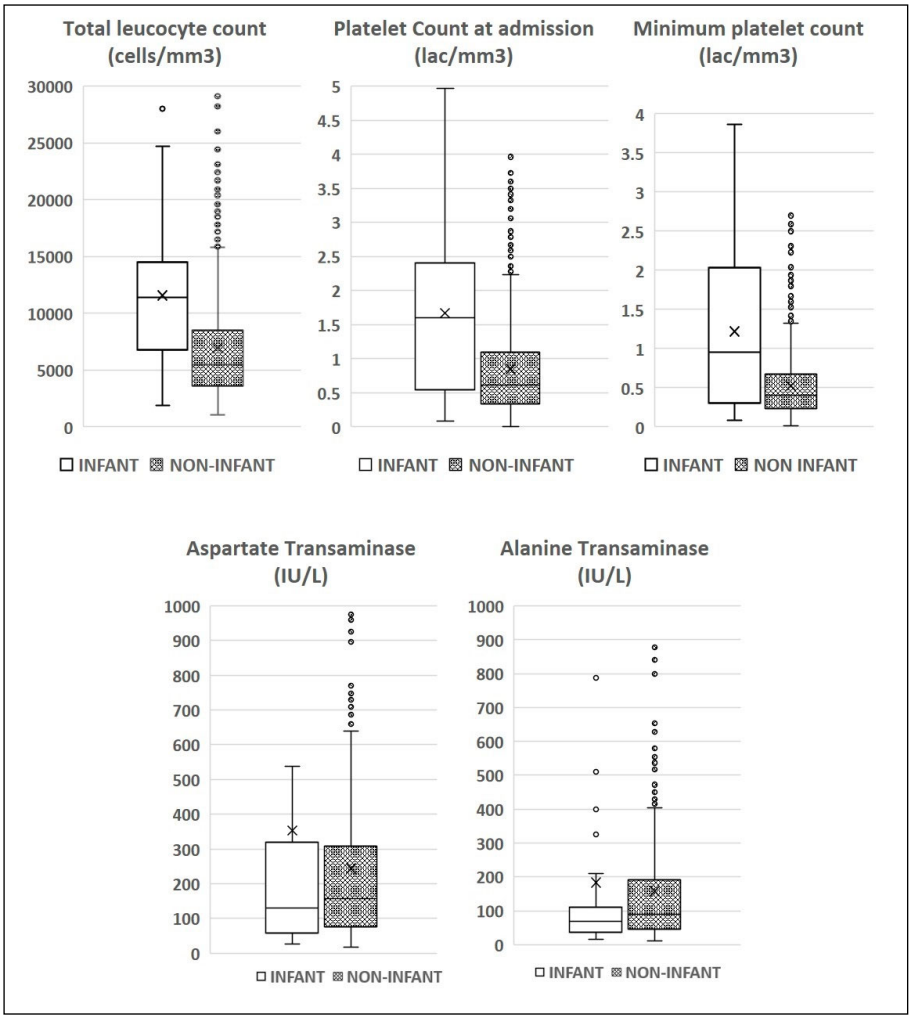

Figure 1. Box and whisker plots comparing total leukocyte count, platelet count, minimum platelet count, aspartate transaminase and alanine transaminase between infants and non-infants.

ber of cases in our study tested positive only for IgM antibodies. Antibody cross-reactivity with other flaviviruses is well known, especially Japanese Encephalitis (JE), which is endemic in our adjoining area[29]. The primary catchment region of our institute does not lie in JE endemic zone; however, possible contamination due to population migration from the endemic regions cannot be ruled out. The routine JE vaccinations administered in these regions may also act as a confounder[30]. This may be viewed as a limitation of our study.

CONCLUSIONS

Our study findings suggest that dengue infection in infants can present like any other acute viral illness. Given the predominance of respiratory, gastrointestinal symptoms and seizure at presentation, a high index of suspicion is warranted. Screening all infants for infection in dengue season may be justified, reducing the empirical use of antibiotics. A very low proportion of infants showed severe symptoms, severe thrombocytopenia and platelet transfusion requirement. Also, there was no mortality in this age group. Thus, our study suggests that infants have an overall milder course of illness due to dengue infection compared to older children.

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Ethics Approval:
The Ethics Committee of the Postgraduate Institute of Child Health, Noida, UP provided approval for the conduct of the study (PGICH- IEC- 2022-05-IM-02, dated 07/05/2022).

Informed Consent:
The consent of patients was waived due to the retrospective nature of the study and to the anonymized nature of collected data.

Authors' Contributions:
D.K. Singh and B.K. Bhakhri conceptualized and designed the study and V. Tyagi and N. Singh drafted the article. R. Prajapati did the acquisition of data and R. Rai and B.K. Bhakhri did the analysis and interpretation of data and made critical revisions related to relevant intellectual content of the manuscript. D.K. Singh, R. Rai and B.K. Bhakhri did the supervision; validation and final approval of the version of the article to be published.

ORCID ID:
B.K. Bhakhri: 0000-0001-5582-8196
V. Tyagi: 0000-0003-4452-0254
R. Prajapati: 0009-0006-4732-6376
D.K. Singh: 0000-0003-0872-1542
R. Rai: 0009-0002-8656-918X
N. Singh: 0000-0003-3593-1326

Conflict of Interest:
The authors declare that there is no conflict of interest.

Availability of Data and Materials :
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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