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Original research article

A Prospective Study on High Sensitivity C-Reactive Protein (hs-CRP) in Children to Distinguish between Severe and Non-Severe Dengue fever

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Abstract

Introduction: Dengue infection can cause a wide spectrum of clinical outcomes. The severe clinical manifestations occur sufficiently late in the disease course, during day 4–6 of illness. Markers of inflammation may be useful biomarkers. There exists a paucity of research on high sensitivity C-reactive protein (hs-CRP) levels in dengue children. We investigated the value of hs-CRP to predict dengue disease severity in children and the difference in hs-CRP levels between dengue patients and healthy controls.

Materials and Methods: This study was conducted in the Department of Paediatrics, Madha Medical College and Research Institute, Chennai (Oct 2021- May 2022).

Results: The study included 31 pediatric dengue patients. The median (IQR) hs-CRP in dengue patients was 46.59 mg/L (34.8, 67.0). The median (IQR) hs-CRP in healthy controls was 0.530 (0.00-2.7) mg/L. The difference was statistically significant ($P < 0.001$). Median (IQR) hs-CRP in severe and non-severe dengue patients were 46.59 (34.77, 68.43) and 46.67 (24.33, 63.79) mg/L respectively which was statistically not significant ($p = 0.85$).

Conclusions: In summary, significantly higher hs-CRP levels were present in dengue children as compared to healthy controls. But there was no significant difference in hs-CRP levels between severe and non-severe dengue patients.

Keywords: Dengue, Severe, Biomarker, hs-CRP, Prognosis, Children

Introduction

Dengue, caused by one of the four dengue virus serotypes (DENV1–4), is globally the most important arboviral infection, in terms of geographic spread and number of infections [1]. An estimated 390 million infections now occur annually in over 100 countries, of which 96 million

manifest as symptomatic dengue cases [2]. The clinical phenotype can vary from a relatively mild self-limiting febrile illness, to severe and occasionally life-threatening symptoms of bleeding, organ impairment, and vascular leakage leading to shock [3]. These severe manifestations occur sufficiently late in the course of the disease around defervescence, which occurs usually on day 4–6 following illness onset, to allow a potential window of opportunity to identify patients who may progress. In areas of dengue transmission, yearly seasonal epidemics occur and can very quickly overwhelm health facilities, with potentially thousands of patients being reviewed daily. As the vast majority of symptomatic infections will result in a benign disease course, the ability to identify patients at high risk of progression, who are likely to benefit from early intervention with supportive therapy, has become the focus of intense research efforts in recent years. Several small studies have attempted to identify biomarkers for dengue that will be cost-effective in resource-limited settings [4]. Recent evidence suggests that markers of inflammation may be useful as biomarkers. Studies have shown higher levels of C-reactive protein (CRP) in severe dengue versus non-severe dengue, with a CRP cutoff level of 30.1 mg/L (AUC, 0.938; 100% sensitivity, 76.3% specificity) [5]. In adult patients in Indonesia on the third day of fever, CRP was higher in those who developed plasma leakage, 10.1 (IQR 4.3– 36.5) vs. 6.3 (IQR 3.0–21.6) mg/L (p = 0.014) [6]. Other studies using highly sensitive (hs) CRP did not find a difference between the severity grades [7]. Higher levels of CRP have also been found in patients with dengue compared to other viral illnesses [8]. A lack of harmonization between these studies has made the results difficult to compare, with varying assay techniques, viral serotypes, age of the participants, immune status, and illness day at the time of sampling. To provide a definitive answer as to the utility of CRP measurement for diagnosis and risk prediction in dengue, these results require validation in a large sample set including early and dynamic sampling, and using a standardized assay. In this study, our objectives were to compare hs-CRP levels between (1) children with severe and non-severe dengue and (2) children with dengue and healthy comparison group.

Materials and Methods

This study was conducted in the Department of Paediatrics, Madha Medical College and Research Institute, Chennai during the period from October 2021 to May 2022.Written informed consent was obtained from the parents/guardians of children for participation. Children in the age group 1-12 years hospitalized with positive NS1 antigen and/or IgM ELISA for dengue were enrolled as cases in the study.

Children with chronic diseases (chronic kidney, heart, lung, gastrointestinal disease) and children with known mixed infections like malaria, typhoid and sepsis were excluded. Hs CRP levels were estimated in healthy children which served as the comparison group . Baseline information about the patients like age, sex, clinical presentation, clinical examination findings, investigation and treatment details were recorded in a case record form. As per 2009 WHO classification [3], dengue cases were classified into two groups: severe dengue (shock, hemorrhage and organ dysfunction) and non-severe dengue (with/without warning signs). A case of severe dengue is defined as a dengue patient with one or more of the following: i) Severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress; ii) Severe bleeding; iii) Severe organ impairment (liver- AST/ALT > 1000 IU/L, CNS-altered sensorium, heart and other organ involvement). Warning signs include: abdominal pain /tenderness, persistent vomiting, lethargy/irritability, clinical fluid accumulation, mucosal bleeds, liver enlargement > 2 cm below costal margin and increase in hematocrit with rapid decrease in platelet counts. Patients were investigated and managed as per WHO guidelines.

Statistical analysis

Data was analyzed using SPSS software. Qualitative data was expressed in proportion and quantitative data was expressed in mean (SD) or median (IQR). Comparison of hs-CRP levels between case and control groups and between severe and non-severe cases was done by Mann-Whitney U test.

Results

The study included 31 pediatric dengue patients. The median (IQR) hs-CRP in dengue patients was 46.59 mg/L (34.8, 67.0). The median (IQR) hs-CRP in healthy controls was 0.530 (0.00-2.7) mg/L. The difference was statistically significant ($P < 0.001$). **Table 1** shows the demographic, clinical and laboratory characteristics of all dengue patients. The age of children ranged from 1-12 years, mean (SD) age being 9.2 (2.67) years. Out of total 31 cases, 14 (45.2%) were males while 17 (54.8%) were females. Nineteen (61.3%) were severe dengue patients. **Table 2** shows the clinical and laboratory parameters in severe and non-severe dengue patients. Median (IQR) hs-CRP in severe and non-severe dengue patients were 46.59 (34.77, 68.43) and 46.67 (24.33, 63.79) mg/L respectively which was statistically not significant ($p = 0.85$). None of the clinical or laboratory characteristics was found to be statistically different between the two groups

Table 1: Baseline characteristics of dengue patients under 12 year of age (n = 31).

Demographics:	
Age, years mean (SD)	9.2 (2.67) (min: 1 yr, max: 12 yr)
Male, n (%)	14 (45.2)
Clinical characteristics: n (%)	
Severe dengue	19 (61.3)
Non-severe dengue	12 (38.7)
Dengue without warning signs	4 (12.9)
Dengue with warning signs	8 (25.8)
Fever	31 (100)
Abdominal pain	22 (71.0)
Vomiting	25 (80.6)
Cough	3 (9.7)
Petechiae	3 (9.7)
Epistaxis	2 (6.5)
Hemetemesis	4 (12.9)

Malaena	3 (9.7)
Flushing	2 (6.5)
Seizures	1 (3.2)
Edema	1 (3.2)
Shock	18 (58.0)
Severe bleed	1 (3.2)
Hepatomegaly	12 (38.7)
Laboratory characteristics: mean (SD)	
Hemoglobin, g/dL	12.6 (2.3)
Total leucocyte count, × 10^3 cells/L	7.2 (5.0)
Platelet count, × 10^9 cells/L	54.2 (52.9)
hematocrit, %	38.5 (7.0)
Serum urea, mg/dL	46.3 (27.9)
Serum creatinine, mg/dL	0.9 (0.5)
SGPT, IU/L	351.5 (736.6)
SGOT, IU/L	453.6 (927 .2)
hsCRP, mg/L	54.89 (33.3)
hsCRP, mg/L Median (IQR)	46.59 (34.8, 67.0)
n (%)	
Raised serum urea	8 (25.8)
Deranged LFT	24 (77.4)
ALT/AST > 1000	2 (6.5)
Pleural effusion	3 (9.7)

Table 2: Comparison of clinical and laboratory parameters between severe (n = 19) and non-severe (n = 12) dengue patients within two days of hospitalization.

Parameters	**Severe dengue**	**Non-severe dengue**	**P value**
Clinical:			
Age, years mean (SD)	9.4 (2.48)	8.8 (3.01)	0.54
Males, n (%);	7 (36.8)	7 (58.3)	0.29
Fever duration, days Mean (SD)	3.79 (1.36)	4.58 (1.78)	0.171
Abdominal pain, n (%);	12 (63.2)	10 (8.3)	0.418
Vomiting, n (%)	16 (84.2)	9 (75.0)	0.653
Rash, n (%)	4 (21.1)	4 (33.3)	0.679
Headache, n (%)	0 (0)	1 (8.3)	0.387
Body ache, n (%)	3 (15.80	4 (33.3)	0.384
Petechiae, n (%)	1 (5.3)	2 (16.7)	0.543
Cough, n (%)	2 (10.5)	1 (8.3)	1.00
Epistaxis, n (%)	1 (5.3)	1 (8.3)	1.00
Hemetemesis, n (%)	2 (10.5)	2 (16.7)	0.630
Malaena, n (%)	3 (15.8)	0	0.265
Flushing, n (%)	2 (10.5)	0	0.570
Hepatomegaly, n (%)	8 (42)	4 (33.3)	0.717
Laboratory;			
hsCRP (mg/L) Median (IQR)	46.59 (34.77, 68.43)	46.67 (24.33, 63.79)	0.85
Hemoglobin, g/dL Mean (SD)	12.51 (2.56)	12.83 (2.04)	0.715
Total leucocyte count; $\times 10^3$ cells/L Mean (SD)	8284 (5891)	5557 (2308)	0.14
Platelet count, $\times 10^9$ cells/L Mean (SD);	67447 (62476)	33100 (21412)	0.038
Hematocrit, % Mean (SD);	37.89 (7.89)	39.0 (5.689)	0.675
Raised Serum urea n (%),	5 (26.3)	3 (25)	1.000
Deranged LFT n (%),	15 (78.9)	9 (75.0)	1.000

Discussion

In this study, the median (IQR) hs-CRP in 31 dengue patients was significantly higher as compared to healthy controls 46.59 mg/L (34.8-67.0) vs.0.530 mg/L (0.00, 2.79). Median (IQR) hs-CRP in severe and non-severe dengue patients were 46.59 (34.77, 68.43) and 46.67 (24.33, 63.79) mg/L respectively which was statistically not significant (p = 0.85).Utility of CRP has been studied in few studies in adults and children as early predictor of severe dengue cases [5,9,10]. CRP is an acute phase reactant and serves as a marker of infection/inflammation. Clinically, it is used to differentiate between viral and bacterial infection, to assess severity of illness and response to treatment. Hs-CRP is being used to assess the level of CRP which has lower range of measurement as compared to conventional CRP. Hs-CRP has been evaluated in children in asthma, nephrotic syndrome [11,12]. However, there is a paucity of research on hs-CRP levels in dengue children. In this study, hs-CRP levels were found to be significantly higher in dengue cases as compared to healthy controls. Kutsuna S, et al. [13] concluded in their study that low CRP suggests dengue fever and is helpful in differentiating from malaria. Ho, et al. [9] in his study observed low CRP values (< 20 mg/dl) as a marker for dengue. In the present study, no significant difference was found in hs-CRP levels between severe and non-severe dengue cases. In contrast to our findings, Chen, et al. [5], in their study in adult dengue patients, observed increasing CRP levels with severity of dengue, mean CRP in DF, DHF I, DHF III were 8.5, 15.2 and 124.5 respectively which was statistically significant (p value < 0.0001). In the same study, CRP was significantly higher in severe dengue as compared to non-severe adult dengue patients. The same study also reported that CRP level was higher in febrile phase as compared to critical phase. In our study most of the patients were admitted in critical phase. This could have altered our finding of no significant difference in hs-CRP between severe and non severe groups. In study by Atukuri SR, et al. [10],CRP was significantly increased in severe dengue cases as compared to non-severe dengue cases. But the limitation of their study was that it had only one case of severe dengue. Small sample size and inability to assess hs-CRP level in early febrile phase are the limitations of our study.

Conclusions

Despite increasing global efforts to reduce the physical and socioeconomic impact of dengue, reliable biomarkers for predicting disease severity remain scarce. This study provides important insight into the association between hs-CRP levels and dengue in children. Our study found significantly higher level of hs-CRP in dengue children as compared to healthy controls. But no significant difference in hs-CRP level could be found between severe and non-severe dengue patients. More studies with good sample size are required to see the hs-CRP level in early febrile phase too.

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