International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 5, No. 1, January-March 2016 Online ISSN: 2250-3137
Print ISSN: 2977-0122

Original Research

The Value of High Sensitivity C-Reactive Protein (hs-CRP) in Distinguishing Severe and Non-Severe Dengue in Pediatric Population

Dr. Ranjana Yadav[1], Dr. Anand Narain Prasad[2], Dr. Anjum Parwez[3], Dr. Neerja Katiyar[4]

[1]Assistant Professor, Department of Paediatrics, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India
[2]Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India
[3]Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India
[4]Assistant Professor, Department of Obstetrics & Gyanecology, Rama Medical College, Kanpur, U.P., India

Corresponding Author:
Dr. Anand Narain Prasad
Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India

Received: 18 February, 2016 Accepted: 12 March, 2016 Published: 18 March, 2016

ABSTRACT
Background: High-sensitivity C-reactive protein (Hs-CRP) has yet to be investigated in pediatric populations with dengue. This study has been developed to assess the efficacy of hs-CRP in detecting severe dengue among pediatric populations. The objectives of this study were to investigate and compare high-sensitivity C-reactive protein (hs-CRP) levels in children diagnosed with dengue and a healthy control group, in addition to distinguishing between non-severe and severe dengue cases.
Methodology: The descriptive cross-sectional investigation involved 45 children younger than 13 years, comprising a dengue-positive group (identified via NS1 antigen and/or IgM ELISA) and a healthy control group, as well as a distinction between severe and non-severe dengue cases.
Result: Median (IQR) high-sensitivity C-reactive protein (hs-CRP) concentrations were 47.36 (35.1, 66.8) mg/L and 0.650 (0.01, 3.1) mg/L respectively in individuals with dengue and healthy controls, demonstrating a statistically significant difference ($p < 0.001$). The median (IQR) hs-CRP levels in patients with severe and non-severe dengue were 47.36 (35.1, 66.8) and 46.62 (26.2, 62.8) mg/L, respectively, indicating a statistically insignificant disparity ($p = 0.846$). High-sensitivity C-reactive protein (hs-CRP) levels were notably elevated in children with dengue compared to those in the healthy control group. However, there was no statistically significant disparity in hs-CRP levels between patients with severe dengue and those with non-severe dengue.
Keywords: High sensitivity CRP, Dengue, Severe, Non-severe, Children

Introduction

Dengue is a mosquito-transmitted illness resulting from four distinct serotypes of the dengue virus. Dengue infection presents diverse clinical manifestations and exhibits a variable disease progression. The clinical manifestations of infection vary from mild viral-like symptoms to severe conditions such as shock, severe hemorrhage, and multi-organ dysfunction syndrome. It is estimated that 100 to 400 million infections occur annually on a global scale [1]. Approximately 500,000 individuals with severe dengue necessitate hospitalization annually, with a significant percentage being children, and approximately 2.5% of those affected succumbing to the illness [2]. Mortality associated with dengue can be mitigated through the prompt identification of severe dengue cases. This can be achieved through two primary approaches: firstly, by consistently observing all individuals suspected of having dengue, and secondly, by recognizing a limited number of dependable early indicators of severe dengue. Frequent monitoring is attainable via the hospitalization of all suspected cases; however, this is not practical as it would place an excessive burden on the healthcare system. Thus, the early identification of

predictors of severe dengue represents a more viable and cost-effective strategy, particularly in developing nations. Several clinical, laboratory, and radiological indicators of severe dengue have been investigated in both adult and pediatric populations. In a retrospective investigation, Gupta et al. [2] determined that the existence of spontaneous hemorrhage, hepatomegaly, indications of capillary permeability such as ascites and pleural effusion, leucopenia below 4000 mm^3, and age exceeding 5 years constituted significant risk factors for shock in pediatric individuals with dengue hemorrhagic fever (DHF). Ho, et al.s [3] executed a study in Taiwan involving 100 children and 481 adults and found that leucopenia, thrombocytopenia, elevated aminotransferases, decreased C-reactive protein (CRP), and prolonged prothrombin time (PTT) were valuable predictive markers for the prompt diagnosis of dengue infection amidst a substantial outbreak in Southern Taiwan. The 2009 WHO classification incorporates warning signs to facilitate the early identification of severe dengue cases; however, the sensitivity and specificity of each warning sign are notably low [4]. C-reactive protein (CRP) has been investigated as a biomarker to differentiate between severe and mild dengue cases in adult patients [5]. A research investigation was carried out among pediatric subjects with dengue to evaluate the relationship between C-reactive protein (CRP) levels and the severity of the illness [10]. Hs-CRP, employed in this research to evaluate CRP levels, exhibits a lower detection threshold compared to traditional CRP measurements. The concentration of hs-CRP has been examined in pediatric populations with asthma, nephrotic syndrome, and type 1 diabetes mellitus. Ramakrishnan N, et al. [6] reported an inverse correlation between hs-CRP levels and asthma control in children. Additionally, Asilewska A, et al. [7] evaluated the levels of hs-CRP in children diagnosed with nephrotic syndrome. Nevertheless, there has been no research conducted on pediatric populations to examine high-sensitivity C-reactive protein (hs-CRP) levels in individuals with dengue fever. Consequently, this research has been designed to evaluate the effectiveness of hs-CRP in identifying severe dengue in pediatric populations. The objectives of this research were to examine and compare high-sensitivity C-reactive protein (hs-CRP) levels among children diagnosed with dengue and a healthy control group, as well as to differentiate between severe and non-severe dengue cases.

Materials and Methods

This descriptive cross-sectional study was conducted in the Departments of Pediatrics and Microbiology of Rama Medical College, Hospital & Research Center, Hapur and Kanpur over a period of three months (from September to November 2015). The written informed consent was obtained from the parents or guardians for participation.

Inclusion Criteria: Children aged 1 to 12 years who were hospitalized with a positive NS1 antigen and/or IgM antibody by ELISA test for dengue were included as cases in this study. **Exclusion Criteria:** Children diagnosed with chronic illnesses such as chronic kidney, lung, heart, or gastrointestinal complications, as well as those with recognized mixed infections including malaria, sepsis, and typhoid were excluded from the study.

Control Group: Serum hs-CRP levels were measured in healthy children serving as controls.

Baseline demographic data of the patients, including age, gender, clinical examination results, clinical presentation, investigative procedures, and treatment specifics, were documented in a case record form. According to the 2009 World Health Organization classification [8], dengue cases were categorized into two groups: severe dengue (characterized by hemorrhage, shock, and organ dysfunction) and non-severe dengue (with or without the presence of warning signs). A case of severe dengue is characterized by a dengue patient exhibiting one or more of the following manifestations: i) Significant plasma leakage resulting in shock (dengue shock) and/or fluid accumulation accompanied by respiratory distress; ii) Severe organ dysfunction (such as liver impairment indicated by AST/ALT levels exceeding 1000 IU/L, central nervous system involvement manifesting as altered sensorium, as well as heart or other organ involvement; iii) Profound bleeding. Indicative signs encompass abdominal tenderness or pain, continual vomiting, irritability or lethargy, mucosal hemorrhages, clinical fluid accumulation, liver enlargement exceeding 2 cm beneath the costal margin, and an elevation in hematocrit accompanied by a swift decline in platelet levels. Patients were examined and treated in accordance with World Health Organization (WHO) guidelines.

Laboratory Procedure: A peripheral venous blood sample (2 ml) was obtained from dengue patients in a plain vial during the initial two days of their hospital admission. Serum was obtained through centrifugation and subsequently stored at -20 ℃ until further analysis. The hs-CRP ELISA was conducted employing a commercially available kit founded on the principles of two-site sandwich enzyme immunoassay (Xema, CRP Ultra EIA, Russia) to evaluate the concentrations of hs-CRP. The murine monoclonal antibody is directed towards the human CRP antigen within the assay. The average absorbance values (OD 450) for each set of calibrators and samples were computed. A calibration curve illustrating optical density (OD) versus C-reactive

protein concentration was constructed to ascertain the high-sensitivity C-reactive protein (hs-CRP) concentrations.

Data Collection and Statistical analysis: The data was examined utilizing SPSS software. Qualitative data was articulated in terms of proportions, while quantitative data was conveyed through means (standard deviations) or medians (interquartile ranges). The Mann-Whitney U test was utilized to compare hs-CRP levels among case and control groups, as well as between severe and non-severe instances.

Result

The research encompassed 54 pediatric individuals diagnosed with dengue. The median (IQR) high-sensitivity C-reactive protein (hs-CRP) level in dengue patients was 47.36 mg/L (35.1, 66.8), whereas the median (IQR) hs-CRP in healthy controls was 0.65 (0.01-3.1) mg/L. The disparity was statistically significant ($P < 0.001$). Table 1 presents the demographic, clinical, and laboratory attributes of all dengue patients. The age of the pediatric participants ranged from 1 to 13 years, with a mean (SD) age of 10.5 (±2.1) years. Among the total 45 cases, 21 (46.6%) were males, and 24 (53.3%) were females. Twenty-eight individuals (62.2%) were classified as having severe dengue.

Table No.1: Baseline characteristics of dengue patients under 13 year of age (n = 45)	
Age (Year) Mean (SD)	10.5 (±2.1)
Male n, (%)	21 (46.6%)
Clinical Characteristic: n (%)	
Severe dengue	28 (62.2%)
Non- Severe dengue	17 (37.8%)
Dengue without warning signs	6 (13.3%)
Dengue with warning signs	12 (26.6%)
Fever	45 (100%)
Abdominal pain	33 (73.3%)
Vomiting	37 (82.2%)
Petechiae	5 (11.1%)
Cough	4 (8.8%)
Hemetemesis	6 (13.3%)
Malaena	5 (11.1%)
Epistaxis	3 (6.6%)
Seizures	2 (4.4%)
Edema	2 (4.4%)
Severe bleed	2 (4.4%)
Shock	27 (60.0%)
Hepatomegaly	18 (40.0%)
Flushing	3 (6.6%)
Laboratory characteristics: mean (SD)	
Hemoglobin, g/dL	12.5 (2.4)
Total leucocyte count, $\times 10^3$ cells/L	7.3 (5.2)
Platelet count, $\times 10^9$ cells/L	53.4 (52.7)
Hematocrit, %	37.9 (6.8)
Serum urea, mg/dL	45.8 (26.9)
Serum creatinine, mg/dL	0.8 (0.4)
SGPT, IU/L	352.6 (34.2)
SGOT, IU/L	454.2 (26.4)
hsCRP, mg/L	55.36 (12.5)
hsCRP, mg/L Median (IQR)	47.36 (35.1, 66.8)
n (%)	
Raised serum urea	12 (26.6%)
Deranged LFT	36 (80.0%)
ALT/AST > 1000	4 (8.8%)

Pleural effusion	5 (11.1%)

Table No. 2 shows the laboratory and clinical parameters in non-severe and severe dengue patients. Median (IQR) hs-CRP in severe and non-severe dengue patients were 47.36 (35.1, 66.8) and 46.62 (26.2, 62.8) mg/L respectively which was statistically not significant (p = 0.846). None of the laboratory or clinical characteristics feature was found to be statistically different between the case and control groups.

Table 2: Comparison of laboratory and clinical parameters between non-severe (n = 17) and severe (n = 28) dengue patients within three days of hospitalization.

Parameters	Severe dengue	Non-severe dengue	P value
Clinical:			
Fever duration, days Mean (SD)	3.84 (1.28)	3.86 (1.62)	0.161
Abdominal pain, n (%)	17 (60.7%)	13 (76.4%)	0.412
Vomiting, n (%)	21 (75.0%)	11 (64.7%)	0.648
Rash, n (%)	6 (21.4%)	7 (41.1%)	0.675
Headache, n (%)	19 (67.8%)	2 (11.7%)	0.384
Body ache, n (%)	18 (64.2%)	9 (52.9%)	0.382
Flushing, n (%)	4 (14.2%)	1 (5.8%)	0.568
Hepatomegaly, n (%)	13 (46.4%)	6 (35.2%)	0.714
Petechiae, n (%)	3 (10.7%)	2 (11.7%)	0.538
Cough, n (%)	4 (14.2%)	2 (11.7%)	1.00
Epistaxis, n (%)	2 (7.1%)	1 (5.8%)	1.00
Hemetemesis, n (%)	4 (14.2%)	2 (11.7%)	0.631
Malaena, n (%)	3 (10.7%)	0 (00%)	0.264
Laboratory:			
hsCRP (mg/L) Median (IQR)	47.36 (35.1, 66.8)	46.62 (26.2, 62.8)	0.846
Platelet count, $\times 10^9$ cells/L Mean (SD);	31200 (28270)	67426 (64302)	0.037
Hemoglobin, g/dL Mean (SD)	12.49 (2.82)	13.14 (2.16)	0.714
Total leucocyte count; $\times 10^3$ cells/L Mean (SD)	8294 (5730)	5564 (2407)	0.037
Hematocrit, % Mean (SD);	37.89 (8.2)	39.42 (5.7)	0.673
Raised Serum urea n (%)	9 (32.1%)	5 (29.4%)	1.00
Deranged LFT n (%),	19 (67.8%)	11 (64.7%)	1.00

Discussion

In this cross-sectional investigation, the median (IQR) high-sensitivity C-reactive protein (hs-CRP) levels in cases were found to be markedly elevated in comparison to those of healthy controls group. The median (IQR) hs-CRP values in patients with severe and non-severe dengue were indicating no statistically significant difference (p = 0.85). The utility of CRP has been examined in several studies involving adults and children as an early indicator of severe dengue cases [3,5,10]. C-reactive protein (CRP) is an acute phase reactant protein that acts as an indicator of inflammation and infection. In clinical practice, it serves to distinguish between bacterial and viral infections, evaluate the severity of illness, and monitor responses to therapeutic interventions. Hs-CRP is employed to evaluate CRP levels, exhibiting a reduced measurement range compared to conventional CRP. High-sensitivity C-reactive protein (hs-CRP) has been assessed in pediatric populations with asthma, nephrotic syndrome, and type 1 diabetes mellitus [7, 8]. No research has assessed hs-CRP levels in pediatric dengue patients. In this investigation, it was observed that hs-CRP levels were notably elevated in individuals with dengue compared to those in the healthy control group. No research has examined the high-sensitivity C-reactive protein (hs-CRP) levels among individuals with dengue fever and a healthy control group. Kutsuna S, et al. [10] determined in their research that a low C-reactive protein (CRP) level indicates the presence of dengue fever and aids in distinguishing it from malaria. Ho et al. [3] in their research noted that low C-reactive protein (CRP) levels (below 20 mg/dl) serve as an indicator of dengue infection. In this investigation, there is no any statistically significant disparity in hs-CRP levels was observed between non-severe and severe dengue cases. In contrast to our results, Chen et al. [5], in their investigation of adult dengue patients, noted a correlation between elevated CRP levels and the severity of dengue, with mean CRP values in Dengue Hemorrhagic Fever I (DHF I), Dengue Fever (DF) and DHF III being 15.2, 8.5 and 124.5, respectively, which was significant statistically (p<0.0001). The same study also found that CRP levels were significantly increased

in patients with severe dengue compared to those with non-severe dengue. Furthermore, the research indicated that CRP levels were elevated during the febrile phase as compared to the critical phase. In our research, the majority of patients were admitted during the critical phase. This might have changed our conclusion of no significant disparity in hs-CRP levels between the severe and non-severe groups. In the research conducted by Atukuri SR, et al. [10], it was found that high-sensitivity C-reactive protein (hs-CRP) was significantly elevated in instances of severe dengue as compared to those of non-severe dengue. However, a notable constraint of their research was the inclusion of only a single instance of severe dengue. The small sample size and the inability to evaluate hs-CRP levels during the initial febrile phase represent limitations of our research. Likewise, in a study performed by Aradhana et al. [11], the median (IQR) hs-CRP in 31 dengue patients was found to be significantly elevated compared to that of healthy controls. Furthermore, the median (IQR) hs-CRP among patients with severe and non-severe dengue showed no statistically significant difference ($p = 0.85$).

Conclusion

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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