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ORIGINAL RESEARCH

The Usefulness of High Sensitivity C-Reactive Protein (hs-CRP) to Differentiate between Severe and Non-Severe Dengue in Children

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Abstract

High sensitivity CRP (Hs-CRP) has not been studied in children with dengue so far. We conducted this descriptive cross-sectional study to compare hs-CRP levels between a group of 31 children under 12 year of age with dengue (positive NS1 antigen and/IgM ELISA for dengue) and healthy comparison group and between severe and non-severe dengue cases. Hs-CRP levels were assessed in sera of hospitalized dengue cases and healthy controls.

Median (IQR) hs-CRP levels were 46.59 (34.8, 67.0) mg/L and 0.530 (0.00, 2.79) mg/L respectively in dengue cases and healthy controls which was statistically significant ($p < 0.001$). Median (IQR) hs-CRP levels 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 ($p = 0.85$). Hs-CRP level was significantly higher in dengue children as compared to healthy controls. But no significant difference in hs-CRP level was found between severe and non-severe dengue patients.

Keywords

High sensitivity CRP, Dengue, Severe, Non-severe, Children

Introduction

Dengue is a mosquito-borne disease caused by 4 different serotypes of dengue virus. Dengue infection has varying clinical manifestations and disease course. Presentation ranges from mild viral-like illness to shock, severe bleeding and multi-organ dysfunction syndrome. An estimated 100-400 million infections occur every year worldwide [1]. Around 500,000 people with severe dengue require hospitalization every year, a large proportion of whom are children and about 2.5% of those affected die [1]. Mortality due to dengue may be prevented by early recognition of severe dengue cases. This can be done in two ways: Firstly, by frequent monitoring of all suspected dengue patients and secondly, by identifying few reliable early predictors of severe dengue. Frequent monitoring is possible by hospitalization of all the suspected cases, which is not feasible as it will overburden the health system. So, identifying early predictors of severe dengue is more feasible and economical option especially in developing countries.

Various clinical, laboratory and radiological predictors of severe dengue have been studied in adults as well in children. In a retrospective study, Gupta, et al.

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[2] concluded that the presence of spontaneous bleeding, hepatomegaly, signs of capillary leakage like ascites and pleural effusion, leucopenia < 4000 mm^3 and age > 5 years were significant risk factors for shock in pediatric patients with dengue hemorrhagic fever (DHF). Ho, et al. [3] conducted a study in Taiwan on 100 children and 481 adults and concluded that leucopoenia, thrombocytopenia, elevated aminotransferases, low CRP and prolonged a PTT were useful predictive markers for early diagnosis of dengue infection during a large outbreak in Southern Taiwan.

Warning signs have been included in WHO classification 2009 for early identification of severe dengue cases but sensitivity and specificity of each warning sign is very low [4]. CRP has been studied as a biomarker to distinguish between severe and mild dengue cases in adults [5]. One study was conducted in children with dengue to assess the correlation of CRP with disease severity [6].

Hs-CRP, being used in this study to assess the level of CRP, has low detection threshold of measurement as compared to conventional CRP. Hs-CRP has been evaluated in children with asthma, nephrotic syndrome and type 1 diabetes mellitus. Ramakrishnan N, et al. [7] found that there is an inverse correlation between hs-CRP levels and asthma control in children. Wasilewska A, et al. [8] assessed the level of hs-CRP in children with nephrotic syndrome. However, no study has been done in children to see hs-CRP levels in dengue patients. So, this study has been planned to see the utility of hs-CRP in identification of severe dengue in children. Objectives of this study were to compare hs-CRP levels between children with dengue and healthy comparison groups and between severe and non-severe dengue cases.

Methodology

Study settings

This descriptive cross-sectional study was conducted in the Departments of Pediatrics and Microbiology of a tertiary care hospital affiliated to a Medical College in the East part of Delhi over a period of 3 months (September- November 2018). Written informed consent was obtained from the parents/guardians for participation.

Participants

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 as controls whose sera were collected as part of postgraduate thesis.

Baseline data collection

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 [9], 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.

Sampling and laboratory analysis

2 mL of peripheral venous blood sample was collected from dengue cases in plain vial within first two days of admission in the hospital. Serum was separated by centrifugation and was stored at a temperature of -20 °C till further testing. The hs-CRP ELISA was done using a commercial kit based on two-site sandwich enzyme immunoassay principle (Xema, CRP Ultra EIA, Russia) to assess the levels of hs-CRP. Murine monoclonal antibody is targeted against human CRP antigen in the assay. The mean absorbance values (OD450) for each pair of calibrators and samples were calculated. A calibration curve of OD versus C-reactive protein concentration was plotted to determine the hs-CRP concentrations.

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

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)

(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.

Discussion

In this cross-sectional 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 [3,5,6]. 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 and type 1 diabetes mellitus [7,8]. No study has evaluated hs-CRP in dengue children. In this study, hs-CRP levels were found to be significantly higher in dengue cases as compared to healthy controls. No study has compared hs-CRP levels between dengue patients and healthy controls. Kutsuna S, et al. [10] concluded in their study that low CRP suggests dengue fever and is helpful in differentiating from malaria. Ho, et al. [3] 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. [6], hs-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 imitations of our study.

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.

Funding Sources

None.

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; × 10^3 cells/L Mean (SD)	8284 (5891)	5557 (2308)	0.14
Platelet count, × 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

Competing Interest

None stated.

Author Contributions

Bineeta Kashyap: Conceptualization, methodology-original draft preparation, supervision, reviewing; Aaradhana: Conceptualization, data collection, data interpretation, original draft preparation, reviewing; Krishna Singhla: Investigation, methodology, proofreading; Rahul Sharma: Data analysis, editing, reviewing.

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