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ASSESSMENT OF PROTEINURIA FOR EARLY DIAGNOSIS AND RISK PREDICTION OF DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME IN DENGUE INFECTIONS

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ABSTRACT

Dengue is the one of most important endemic disease in India which is getting more common in recent years, affecting all age groups. Following an initial febrile period, a small proportion of infected patients develop a vasculopathy, who have a risk for severe vascular leakage and shock. Since there is no treatment available, close clinical monitoring and careful fluid therapy is the only way of management for those with severe dengue disease, i.e., dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Differentiation between dengue and other common febrile illnesses is difficult during the early febrile phase, and risk prediction for development of shock is poor.The presence of proteinuria is recognized as a useful early predictor for subsequent complications in a number of other disorders with vascular involvement.Significant proteinuria occurs in dengue shock syndrome and it is possible that proteinuria in the early-phase may be helpful for identification of patients who are likely to develop severe complications in dengue. Predicting disease severity is important in triaging patients requiring hospital care. We aim to study the value of proteinuria in predicting the development of dengue haemorrhagic fever (DHF), utility of urine dipstick test as a rapid prognostic tool.We measured formal urine albumin to creatinine ratios (UACRs) in daily samples obtained from a large cohort of Patients with dengue infections confirmed in by dengue RT-PCR or NS1 antigen detectionrecruited at SBMCH. Dengue cases had median fever duration of 6 days at enrolment. DHF was diagnosed in cases according to the WHO 1997 guideline. Dengue fever (DF) patients were predominantly younger. Compared to DF, DHF cases had significantly higher peak urine protein creatinine ratio (UPCR) during clinical course (26 vs. 40 mg/mmol; p, 0.001). thus Proteinuria measured by a laboratory-based UPCR test may be sensitive and specific in prognosticating adult dengue patients.

KEYWORDS:Dengue, DHF , DSS**, Proteinuria,** UCPR

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INTRODUCTION

Dengue is the most prevalent mosquito-borne viral disease in South East Asia[1] spread by aedes mosquito .It affects millions of people in tropical and subtropical regions. Itcauses significant morbidity and mortality[2] which can be prevented by the early detection of dengue fever (DF) and monitoring for signs of progression to severe disease namely dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS)[3].Many studies have been done to combine clinical and simple laboratory tests to predict DHF/DSS. In Singapore, by evaluating clinical bleeding, hypoproteinemia, lymphopenia and elevated serum urea, an algorithm was derived and validated to predict adult DHF[4]. In resource-limited settings the need for serum protein and urea reduces the usage of such algorithm[5]. A similar algorithm using monocyte, leukocyte, and platelet counts with serum haematocrit predicted DSS in Thailand[6].In this study we assess the use ofproteinuria for early diagnosis and risk prediction of dengue hemorrhagic fever/dengue shock syndrome in dengue infections.

Aim and Objectives

Objectives

- To evaluate the clinical profile of dengue patients
- Toassess the use ofproteinuria for early diagnosis and risk prediction of dengue hemorrhagic fever/dengue shock syndrome in dengue infections.

METHODOLOGY

This study was conducted in SREE BALAJI MEDICAL COLLEGE, CHENNAI. 160 patients with positive dengue NS1 recruited from July 2015 to February 2016.Informed consent was taken from every subject. All data were anonymised. This study was approved by the SBMCH ethics committee.(Approval no: Ref.No.002/SBMC/IHEC/2015/166). Written informed consent was taken from every subject. All data were anonymised.

Inclusion criteria

Adult patients (>18 years) with confirmed dengue fever by NS1 antigen [7] were enrolled at SBMCH between July 2015 to feb 2016.

Exclusion criteria

Subjects with pre-existing renal disease, systemic hypertension, diabetes were excluded from the analysis.

Method

Dengue positive patients were followed up daily during the acute period and subsequently 21–30 days from enrolment. Demographic and epidemiological data were collected at enrolment and symptoms and signs were recorded at each visit. Hematology and biochemistry tests were performed daily.Urine sample collection and testing Spot urine collection was done by the mid-stream clean catch method on each study day. Using MicralTestR presence of protein in the urine was checked immediately. Urine protein creatinine ratio (UPCR) was done to confirm the amount of proteinuria. Clinically significant proteinuria was defined as UPCR>20 mg/mmol in line with criteria from the US National Kidney Foundation [8].Subjects must have fever or history of fever, haemorrhagic manifestations, thrombocytopenia, and plasma leakage to fulfil DHF. The day that the subjects fulfilled DHF definition were duly noted. For DSS, DHF cases required either (i) tachycardia with narrow pulse pressure or (ii) systolic blood pressure (SBP), 90 mmHg[9].

Statistical analysis

For descriptive analyses, median, 5^{th} and 95^{th} percentiles (pctl) were used for continuous variables. Number and percentage were used for categorical variables. Chi-square and Fisher's exact tests were used to compare categorical variables between DF and DHF groups. A p-value of less than 0.05 was considered significant.Using receiver operating curve (ROC) we studied the cut-off point of UPCR peak value analysis to obtain the best sensitivity and specificity in differentiating between DF and DHF. To study the role of UPCR in discrimination of DHF, we used the data available at the time of initial presentation as well as throughout the entire illness. We assessed trends of UPCR by defervescence day for DF and DHF The day of defervescence was taken as day 0, and one day before as day — 1 and one day after as day +1. In a separate analysis by DHF onset day, the day of DHF was taken as day 0.

RESULTS

Participants

There were 160 subjects with positive dengue NS1 recruited from July 2015 to February 2016. Mean age was 36 years age and 75 %(120) were males. Thirty eight percent (61) of subjects were treated as inpatient in the entire course of the illness.

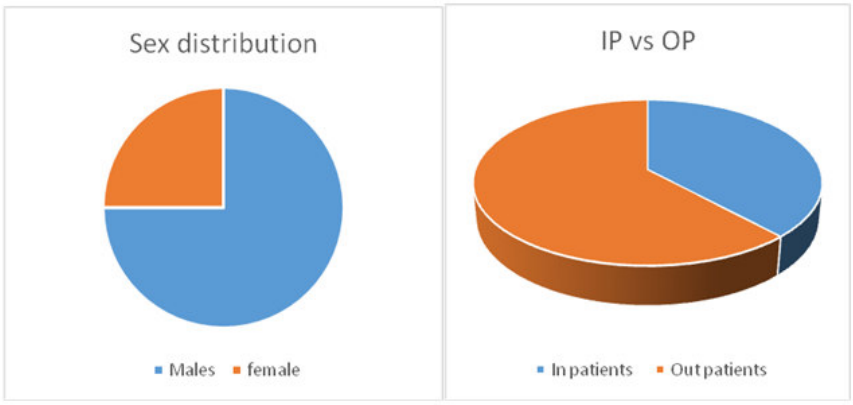

Figure 1
Graph I – Patient distribution

Clinical outcomes
Out of the 160 patients, 32 (20%) had DHF out of which 10 of which were diagnosed with DHF at enrolment visit. The rest of the DHF patients came from the DF patients that progressed to DHF during the course of their illness. Three out of DHF cases had DSS. There were no fatalities.

Proteinuria between DF and DHF patients
Table 1 shows the differences in UPCR values among DF and DHF patients. On comparing DF patients were younger and were mostly seen in the outpatient setting with higher platelet levels than DHF patients. DHF patients had significantly higher peak levels of proteinuria than DF patients; 81% (26) of DHF cases versus (77) 60% of DF cases had significant UPCR>20 mg/mmol. Both groups of patients developed maximum proteinuria at median of 7th day of illness. Patients in the DHF group showed significantly increased proteinuria one day before the onset of DHF. In DF and DHF, before the third day of illness, the UPCR level patients were similar. The two groups showed significantly different trends of proteinuria between days 4 and day 7. The DHF group showed rapidly increased proteinuria versus DF group, whose proteinuria rapidly decline by day 7.

Table 1
Patient characteristics and laboratory parameters.

Dengue postive	DF - 160	DHF – 32 (20%)	P value
Age	36 (20-45)	44(20-60)	<0.001
Male	120	25	0.42
Inpatients	61 (38%)	24	<0.001
UPCR values			
UPCR peak value	26.5(10-88)	42(15-250)	<0.001
UPCR peak illness day	7(4-10)	7 (5-9)	0.40
Significant UPCR ($20 mg/mmol)	75	29	<0.001
Significant UPCR onset as illness day	7 (4-9)	7 (5-9)	<0.001
UPCR peak value before DHF		38(12-250)	0.40
Corresponding laboratory values at peak UPCR			
Hematocrit %	45(37-49)	45(37-49)	0.35
Platelet, x10^A9/Liter	90 (44-207)	55(18-273)	<0.001

DISCUSSION

The two dreaded complications of dengue fever, Dengue haemorrhagic fever and dengue shock syndrome may result in significant morbidity and mortality in adult patients. So Early prediction of complications of dengue might help to have a close monitoring of the patients and improved management of the cases to improve clinical outcome of the patients [10].In dengue infection, proteinuria and Hypoalbuminemiaare known to occur[2]. Altered filtration of the glycocalyx is believed to be the pathophysiologic mechanism causing this[11] asNS1 in dengue virus[12] is known to attach to heparan sulphate, which is part of the glycocalyx.we observed that the patients likely to develop DHF could be identified by peak UPCR distinguish from those who did not and at day 7 of the illness peak UPCR occurred. One day before defervescence a significant increase in proteinuria was seen which corresponded to one day before the development of DHF. Patients with impending DHF and DSS has significantly higher proteinuria than patients with uncomplicated DF. Time course analysis of daily follow-up in this prospective study showed that the discriminatory value of proteinuria was not evident in the early febrile period but it is discriminatory between days 4 and 7, just before defervescence when maximal plasma leakage classically occurs.There were many similar studies evaluated proteinuria as an indicator to predict dengue severity[13-15] which yielded similar results to ours.They show that using UPCR adjusted for age and illness day had a sensitivity of 76% and specificity of 77% for predicting DHF, while combination it with white blood cell count, serum hematocrit, platelet count,

serum protein and bleeding had a sensitivity of 92% and specificity of 80%. Some of these studies included both chidren and adults while ours included only adults.Our study was limited by a less number of DHF and DSS patients and including only adult patients.

CONCLUSION

The identification of early onset and/or severity of urinary protein leak in dengue patients using a laboratory-based UPCR test can be a useful predictor for the subsequent development of DHF and DSS as the onset and peak proteinuria was significantly associated with subsequent development of DHF in both ambulatory and hospitalized adult dengue patients. Daily UPCR may be a useful, sensitive and specific prognostic tool in association with clinical parameters to help triage patients requiring hospital care.

CONFLICT OF INTEREST

Conflict of interest declared none.

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