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Original Research Article

Utility of Urine Protein Creatinine Ratio and Proteinuria as an early Indicator to Predict the Disease Severity and Outcome in Paediatric Dengue Fever: Prospective Study

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Abstract

Objective: The study was undertaken to establish early predictors of disease severity viz urine protein creatinine ratio (UPCR) and proteinuria in children with dengue. **Material and Methods**: A prospective study was conducted in the Department of Paediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India for 15 months. Children aged less than 14 years, hospitalized with clinical features of dengue and testing positive serology (NS1, IgM) were included in the study. All enrolled children were assigned according to urine protein creatinine ratio into 4 groups viz< 0.5, 0.5-1, 1-3, 3. **Results**: All of the 100 children with dengue fever were classified according to UPCR into 4 groups. It was observed that 37 % had UPRC <0.5, 23% had 0.5-1.0, 27% had 1-3 and 13% children had UPRC >3. UPRC was inversely proportional to age and had no association with gender. There was a positive correlation between UPRC and the severity of illness in dengue fever. **Conclusion**: The usage of both UPCR as well as proteinuria estimation in all children afflicted with dengue fever as a screening device for hospitalization, management and prognostication.

Keywords: Pediatric Dengue Fever, Urine Protein Creatinine Ratio, Proteinuria, Prognostic Indicators, Predictor Tools

Introduction

Dengue is the most prevalent mosquito-borne viral disease worldwide[1]. A majority of the infections are asymptomatic or result in a mild febrile illness, but the dengue virus (DENV) is also capable of producing a life-threatening disease. The main form of severe dengue is characterized by plasma leakage with or without bleeding, which may lead to circulatory collapse, called dengue shock syndrome. The course of dengue illness can be divided into three main phases: the febrile phase, the critical phase and the recovery phase. Severe clinical disease manifestations occur during the critical phase which begins around day 4–7 after the onset of fever and lasts usually 48–72 hours. During the critical phase, the condition of patients can improve or worsen rapidly; requiring careful monitoring by care givers. Early clinical management based on fluid replacement therapy reduces the morbidity and mortality associated with severe dengue[2]. The major obstacle for an

effective clinical management of dengue is the inability to accurately predict, at an early stage of infection, which patients are likely to develop a severe form of the disease. There is a need for simple, effective and cheap tests to identify patients at risk and guide triage. Wills et al. observed an increase of urinary protein clearance due to the increase in systemic vascular permeability that occurs in severe dengue. Subsequently, it has been proposed that a simple urine protein excretion screening test could be indicative of the severe form of dengue and therefore guide the triage and monitoring of the patients with suspected dengue infection[3].

The current study was conducted to establish an indicator, in the form of urine protein creatinine ratio(UPCR) and significant proteinuria, to predict the disease severity and outcome as well as enable management in paediatric patients with dengue fever.

Material and Methods

A prospective study was conducted in the Department of Paediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India for 15 months, after taking the approval of the protocol review committee and institutional ethics committee.

Inclusion Criteria

1. Children aged less than 14 years,
2. Presented with clinical warning signs of dengue or severe dengue
3. Testing positive serology (NS1, IgM)

Exclusion criteria

Dengue without warning signs

Methodology

On admission basic parameters such as age, sex, weight and historical data were recorded. Detailed general and systemic examination was done. The clinical features of dengue fever were noted and patients were managed according to WHO guidelines of disease severity as shown in Table 1. The patients were placed in three categories for case management viz. A, B, C after a patient had fulfilled the inclusion criteria for dengue fever. The laboratory investigations for all the patients were recorded. These include dengue serology by rapid solid phase immunochromographic test for quantitative detection of dengue NS1 Ag and differential detection of IgM and IgG Ab. In addition, hemoglobin, packed cell volume, platelet count, ultrasound abdomen and chest x ray were carried out. Urine protein creatinine ratio (urine protein tested by pyrogallol red method and creatinine by modified Jaffe's method) was carried out on confirmation of diagnosis of dengue fever. Protein concentration in urine was obtained by measuring the absorbance at 600nm.Coagulation profile, renal & liver function tests as well as serum electrolytes were studied as per clinical condition. Investigations were repeated if the initial results were abnormal or if there was clinical deterioration. This was done within 24 hours of instituting treatment if the initial report was abnormal. All enrolled children were assigned according to urine protein creatinine ratio into 4 groups viz< 0.5, 0.5-1, 1-3, 3.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages. Test applied for the analysis was chi-square test. The level of confidence interval and p-value were set at 95% and 5%.

Results

A total of 100 children include in this study. Of these 20 were infants, 30 between 1-8 years and 50 children were above 8 years of age of which 70 were boys and 30 girls.

All the patients were grouped according to the ratio as <0.5, 0.5- 1.0, 1.0-3.0 and >3.0.

37% of children had UPCR of less than 0.5. 23% had UPCR of 0.5-1 and 27% had 1-3 of children and 13 % had UPCR of more than 3.0 at admission.

Table 1: Age vs UPRC Distribution

Age/UPCR	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
<1year	2(10%)	3(15%)	5(25%)	10(50%)	20(100%)
1-8year	13(43.33%)	2(6.67%)	13(43.33%)	2(6.67%)	30(100%)
>8year	22(44%)	18(36%)	9(18%)	1(2%)	50(100%)
Total	37	23	27	13	100

X^2=26.61, p<0.05

The study population was divided into 3 groups according to age and compared with UPRC as shown in Table 1. In our study population, 20% were infants, 30% in the 1-8 years group and 50% were over 8 years of age. When the association of UPRC with age was studied, it was seen that occurrence of high UPRC in the dengue affected population was inversely proportion to age (p<0.05).

Of the 70 boys and 30 girls in the study, 30 boys and 12 girls had UPRC of <0.5, 18 boys and 11girls had values of 0.5-1.0, 13 boys &4 girls -1.0-3 and 9 boys and 3 girls had ratios of >3. There was no statistically significant difference in UPRC between males and females (p=0.601).In this study, it was observed that UPCR values were found to be directly proportional to increasing severity of disease. This association was statistically significant (p =0.018).

Table 2: Bleeding manifestations during course of illness

No. of children with bleeding manifestations	**UPCRR<0.5**	**0.5-1.0**	**1.0-3.0**	**>3.0**	**Total**
Yes	0	2	3	7	12
No	37	21	24	6	88

X^2=8.26, p<0.05

Table 2: In this study, 12 children had bleeding manifestations during course of illness, among which 58.33% had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations (p<0.05)

In this study, 37 children had third space collections, in which 22(59.45%) children had UPCR > 1. The association of occurrence of effusions with UPCR was statistically significant (p=0.041)

Table 3: UPCR vs Inotrope Usage

Inotropes	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
Yes	3	2	8	7	20
No	34	21	19	6	80
Total	37	23	27	13	100

X^2=4.31, p<0.05

Table 3: In this study, 20% children required inotropes, among which 40% had UPCR 1-3 and 35%>3. Only 15% children with UPCR < 0.5 required inotropes. It was observed that cases who needed inotropes had higher UPCR and this association was statistically significant (p=0.004).

60 children required transfusions (blood and blood products) during the hospital stay, among which 30% had UPCR <0.5 and 40% had UPCR > 3. The association was statistically not significant (p=0.239).

Table 4: UPCR vs Outcome

Outcome	<0.5	0.5-1.0	1.0-3.0	>3	Total
Discharge	37(39.36%)	23(24.46%)	25(26.60%)	10(9.57%)	95(95%)
Death	0	0	2(40%)	3(60%)	5(5%)

X^2= 8.578, p= 0.029

Table 4: The final outcome was noted as discharged or death in each group. We had 5 deaths in our study, in which 3 children had UPCR>3 and 2 had UPCR 1-3. All children with UPCR <1 were cured and discharged. The association of raised UPCR with mortality showed a positive correlationand was statistically significant. (p =0.029)

Table 5: Significant Proteinuria vs Outcome

Proteinuria/ outcome	<100	100-300	>300	Total
Death	3(60%)	2(40%)	0	5
Discharge	88(92.63%)	4(4.21%)	3(3.16%)	95

X^2= 7.243, P = 0.21

Table 5: The proteinuria in urine sample was quantified by pyrogallol test, the laboratory standard value of which was 100mg/dl. Depending on degree of proteinuria, all dengue serology positive children were divided into three groups viz<100, 100-300 and >300 mg/dl.

In our series, 5 deaths occurred due to dengue, among which 3 children had proteinuria < 100mg/dl and 2 child had proteinuria >100mg/dl. The association was statistically significant. (p = 0.021)

Discussion

Dengue fever is a global illness which is of particular concern in the developing world. In certain areas, it is endemic and associated with considerable morbidity and mortality particularly in the pediatric population. Hence its early diagnosis and prediction of complications becomes exceedingly important. This study was undertaken to establish the significance of early predictor markers viz UPCR and proteinuria in childhood dengue fever.

A total of 100 children include in this study. Of these 20 were infants, 30 between 1-8 years and 50 children were above 8 years of age. These findings are similar to the observation of Graham et al.[5] We did not find any difference in its incidence according to gender. However there are some reports of a higher incidence occurring in males[6].

Urine protein creatinine ratio was checked and categorized in all these children at admission. Our study revealed an inversely proportional association of UPCR with age which was statistically significant. In 1995, Garcia et al observed proteinuria in 22% of dengue fever patients, 38% of whom had it within the first 4 days of the onset of constitutional symptoms[7]. They performed serial proteinuria and correlated the peak proteinuria with day of illness. Our findings were consistent with those of Farhad F. Vasanwala, Tun Linn Thein, Yee-Sin Leo, Victor C. Gan, Ying Hao, Linda K. Lee, David C[8-9] who did a study on Predictive Value of proteinuria in dengue patients and concluded that proteinuria measured by a laboratory-based UPCR test may be sensitive and specific in prognosticating dengue patients[10].

We found a positive association between occurrence of bleeding manifestations and UPCR, which was statistically significant ($p < 0.01$). However the occurrence of coagulopathies did not correlate with altered UPCR. 60 children required transfusions (blood and blood products) during the hospital stay, among which 30% had UPCR <0.5 and 40% had UPCR > 3. The association was statistically not significant($p=0.239$). While bleeding manifestations have been well reported in dengue fever, to our knowledge, no previous published studies showing the correlation of bleeding manifestations and coagulopathies with elevated urine protein creatinine ratio in children areavailable[11-13].

In this study, we observed that there is a significant association for occurrence of third space collection and UPCR (p value= 0.041). There was a positive correlation of UPCR and requirement of inotropic support in our study; we observed that In this study, 20% children required inotropes, among which 40% had UPCR 1-3 and 35 %>3. Only 15% children with UPCR < 0.5 required inotropes. It was observed that cases who needed inotropes had higher UPCR and this association was statistically significant($p=0.004$).

We had 5 deaths in our study, in which 3 children had UPCR>3 and 2 had UPCR 1-3. All children with UPCR <1 were cured and discharged. The association of raised UPCR with mortality showed a positive correlation andwas statistically significant. ($p =0.029$).

Some of the other studies in adult population too have established a positive correlation between the severity of disease and raised UPCR[14-15]. However in them the mortality correlation with UPCR has not been established as in our study.

We also studied the significance of proteinuria and its association with disease severity in children with dengue fever. While we could not find any significant correlation of proteinuria with disease severity, there was a positive association of significant proteinuria with mortality which was statistically significant ($p<0.05$). Other studies have reported renal involvement and its aftermath particularly in dengue shocksyndrome[16-17].

Conclusion

Given the increase occurrence of dengue fever and its associated complications, the need of early predictors of disease severity are important. Such markers have not been well studied in the paediatric population. UPRC and proteinuria assessment are easy to perform and inexpensive tests. This study found UPRC to be an accurate marker in predicting disease severity, third space loss, bleeding manifestations, need of inotropes and adverse outcome in children with dengue fever. Significant proteinuria was found to be a useful marker in predicting adverse outcomes. We therefore recommend the usage of both UPCR as well as protein uria estimation in all children afflicted with dengue fever as a screening device for hospitalization, management and prognostication.

Reference

1. Brady Oliver J, Gething Peter W, Bhatt Samir, Messina Jane P, Brownstein John S, Hoen Anne G, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoSNegl Trop Dis 2012;6(8): e1760.
2. Special Programme for Research and Training in Tropical Diseases, World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention, and control. New ed. Geneva: TDR: World Health Organization; 2009.
3. Wills BA, OraguiEE, Minh DN, Thi LH, Vinh CN, Farrar JJet al. Size and charge characteristics of the protein leak in dengue shock syndrome. J Infect Dis 2004;190(4):810-8.
4. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-tocreatinine ratio over albumin concentration. Diabetes Care 1999; 22:307-13
5. Graham RR,Juffrie M,Tan R et al. A prospective seroepidemiologic study on dengue in children four to nine years of age in Yogyakarta, Indonesia 1995-1996.Am J Trop Hyg 1999Sep;61(3):412-19.
6. Wali JP, Biswas A, Handa R, Aggarwal P, Wig N et al: Dengue hemorrhagic fever in adults: a prospective study of 110 cases. Top Doct1999,29:27-30.
7. World Health Organisation. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: WHO ; 21997.
8. Yip WCL. Dengue haemorrhagic fever: current approaches to management. Medical Progress, 1980, 7:13-15.
9. Vasanwala FF, Puvanendran R, Ng J M, Suhail S M Two cases of self-limiting nephropathies secondary to dengue haemorrhagic fever Singapore Med J 2009;50(7):e253.
10. Vasanwala FF, Puvanendran R, Fook-Chong S, Ng JM, Suhail SM, et al. Could peak proteinuria determine whether patient with dengue fever develop dengue hemorrhagic/dengue shock syndrome?–a prospective cohort study. BMC Infect Dis2011:11:212-15.
11. Lum LCS et al., Risk factors for hemorrhage in severe dengue infection. Journal of Pediatrics, 2002,140:629-31.
12. Wills BA et al., Coagulation abnormalities in dengue hemorrhagic fever: Serial investigations in 167 Vietnamese children with dengue shock syndrome. Clinical Infectious Diseases,2002,35:277-85.
13. Rigau-Pérez JG et al., Dengue and dengue haemorrhagic fever. Lancet,1998,352:971-77.
14. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. Southeast Asian Journal of Tropical Medicine and Public Health, 1987,18(3):392-97.
15. Vasanwala FF, Thein T-L, Leo Y-S, Gan VC, Hao Y, et al. (2014) Predictive Value of Proteinuria in Adult Dengue Severity. PLoSNegl Trop Dis 8(2):e2712.
16. Wills BA, Oragui EE, Minh DN, Loan HT, Chau NV, et al. Size and Charge

Characteristics of the Protein Leak in Dengue Shock Syndrome. J Inf Dis 2004;190(4):810-18.
17. Lumpaopong A, Kaewplang P, Thirakhupt P, Chamnanvanakij S, Srisuwan K, Pongwilairat N, Chulamokha Y: Electrolyte disturbances and abnormal urine analysis in children with dengue infection. Southeast Asian J Trop Med Public Health 2010,41:72-76.