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A study establishing correlation of proteinuria and urine protein/creatinine ratio with disease severity in pediatric dengue fever

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Abstract

Dengue fever has emerged as a major health problem globally with several complications occurring which lead to increasing morbidity and mortality particularly in children. It has therefore become important to establish accurate, easy to perform predictors of disease severity to enable timely management and prevent associated complications. Such markers have not been well researched in the paediatric population. The study was undertaken to establish early predictors of disease severity viz urine protein creatinine ratio (UPCR) and proteinuria in children with dengue. All of the 76 children hospitalized with dengue fever were categorized according to disease severity as per WHO guidelines. Of these, 25% had category 1 disease, 36.8% had category 2 and 38.2% category 3 disease. All children were classified according to UPCR into 4groups. It was observed that 34.2% had UPRC <0.5, 26.3% had 0.5-1.0, 26.3% had 1-3 and 13.2% 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. The association of occurrence of bleeding manifestations, requirement of inotropes and outcome with UPCR was statistically significant. Significant proteinuria had a statistically significant association with mortality, but did not correlate well with disease severity. Thus both UPCR and proteinuria assessment appear to be useful tools for deciding hospitalization, management as well as prognostication in childhood dengue fever.

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

Introduction

Dengue is an Arboviral infection affecting humans and represents a major global public health issue. In the developing world, its incidence is increasing steadily and in many places it has become an endemic problem. Dengue fever in children is associated with many challenges as well as considerable mortality and morbidity. The risk factors for development of severe disease are poorly characterized and consequently uncomplicated cases are frequently hospitalized for observation during the critical phase for capillary leakage syndrome, thereby increasing the financial cost to patients. Therefore improvements in early diagnosis and risk prediction for severe disease are urgently needed, particularly with respect to identification of simple clinical and/ or laboratory indicators that are practical and affordable for use in resource poor countries. This would enable appropriate and early intervention. Ideally, the test should be cheap, fast, easy to perform, highly sensitive and specific.

The presence of microalbuminuria has been postulated as potential risk predictor for severe dengue, but there is little information on the magnitude, timing of onset, or evolution of urinary protein excretion during infection. Moreover, 24 hour urinary albumin measurements are cumbersome and time consuming to perform. But measurement of spot urine protein estimation as well as urine protein to creatinine ratio is a more practical and therefore readily acceptable alternative.(1) While it has been studied in adults with dengue, its usefulness as a predictor tool has not been well tested in pediatric population. 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.

Aims of the Study

1. To correlate urine protein creatinine ratio with severity of illness in children diagnosed to have Dengue fever.
2. To assess whether proteinuria could be used as a predictor of disease progression to severe illness.

Methodology

The present study was a hospital based, serially enrolled, prospective one which was carried out between June 2013 to May 2015 at a tertiary care children hospital at Hyderabad. Children aged 1 month to 18years, hospitalized with clinical features of dengue and testing positive serology (NS1, IgM) were included in the study. Those babies who had clinical features of dengue but with negative serology and those with preexisting renal disease were excluded. Informed consent was obtained from the parents for the study which was approved by the Hospital Ethics& Research Committees.

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 Jaffes 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.

Data obtained was analysed using SPSS software – version 19. Outcomes were tested using the Chi-square test.

Results and Analysis

All hospitalized children aged 1 month to 18years presenting with clinical features of dengue and testing positive serology between June 2013 and May 2015, were enrolled in the study. A total of 76 children met the inclusion criteria. Of these 18 were infants, 10 between 1-5 years and 48 children were above 5years of age of which 45 were boys and 31 girls. All enrolled cases were categorized according to disease severity as per WHO guidelines.[(2)] In our study out of 76 cases, 19 children had category A disease, 28 category B and 29 had category C disease.

A. Urine Protein Creatinine Ratio: All cases enrolled were studied for UPCR at admission. These were grouped according to the ratio as <0.5, 0.5- 1.0, 1.0-3.0 and >3.0. 34.2% of children had UPCR of less than 0.5. 26.3% each had UPCR of 0.5-1 and 1-3. 13.2% of children had UPCR of more than 3.0 at admission.

1. **Age vs UPCR Distribution:** The study population was divided into 3 groups according to age and compared with UPRC as shown in Table 2. In our study population, 23.7% were infants, 13.1% in the 1-5 years group and 63.2% were over 5years 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. This difference was statistically significant(X^2=25.11, P<0.01).
2. **Gender vs UPCR:** In all the cases studied, UPCR values were compared according to gender. Of the 45 boys and 31 girls in the study, 15 boys and 11girls had UPRC of <0.5, 10 boys and 10girls had values of 0.5-1.0, 14 boys & 6girls -1.0-3 and 6boys and 4 girls had ratios of >3. There was no statistically significant difference in UPRC between males and females (p=0.638).
3. Disease Severity vs UPCR as per WHO classification of dengue, enrolled cases were categorised into 3 groups viz dengue fever, dengue fever with warning signs and severe dengue (Table 3). 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 = 0.024).
4. **Bleeding Manifestations and UPCR:** The association of bleeding manifestations and urine protein creatinine ratio is shown in Fig. 1. In this study, 9 children had bleeding manifestations during course of illness, among which 55.6% had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations (p<0.05).
5. The association of deranged coagulation profile and UPCR was studied. Among 76 children, 50% had deranged coagulation profile. Among these 21% had UPCR >3. 26.3% children with UPCR 1-3 had deranged coagulopathy and 34.2% children with deranged coagulopathy had UPCR <0.5. The association was statistically not significant. (p=0.146).
6. **Third Space Collections and UPCR:** The correlation of UPRC with the occurrence of third space collections is shown in Fig. 2. In this study, 29 children had third space collections, in which 58.6% children had UPCR > 1. The association of occurrence of effusions with UPCR was statistically significant (p =0.039).
7. **Inotropes vs UPCR:** The association of inotropes usage and UPCR is shown in Fig. 3. In this study, 17.1% children required inotropes, among which 38.5% had UPCR 1-3 and an equal percentage>3. Only 15.4% 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=0.007).
8. **UPCR vs Blood and Blood Product Usage:** The requirement of blood products and its association with UPCR was studied. 34 children required transfusions (blood and blood products) during the hospital stay, among which 26.4% had UPCR <0.5 and 20.6% had UPCR > 3. The association was statistically not significant (p=0.255).
9. **Outcome vs UPCR:** The final outcome was noted as discharged or death in each group. We had 3 deaths in our study, in which 2 children had UPCR>3 and one had UPCR 1-3. All children with

UPCR <1 were cured and discharged(Table 4). The association of raised UPCR with mortality showed a positive correlation and was statistically significant. (p =0.033)

Table 1: **WHO clinical criteria of disease severity in dengue fever[(1)]**

Category A **Probable Dengue** (Live in/ travel to dengue endemic area. Fever and 2 of the following criteria)	**Category B** **Lab Confirmed Dengue**	**Category C** **Dengue Shock Syndrome** Severe plasma leakage leading to Shock
Nausea, vomiting,	Abdominal pain or tenderness	Fluid accumulation with respiratory distress
Aches and pains	Persistent vomiting	Severe bleeding as evaluated by clinician
Rash	Clinical fluid accumulation	Severe organ involvement
Tourniquet test positive	Mucosal bleed	
Leucopenia	Lethargy; restlessness	
Any warning signs	Liver enlargement >2cm	
	Laboratory: Increase in HCT concurrent with rapid decrease in platelet count	Liver: AST or ALT ≥1000 IU/dl CNS: Impaired consciousness Heart and other organs

Table 2: Age vs UPRC Distribution

Age/UPCR	**UPCRR<0.5**	**0.5-1.0**	**1.0-3.0**	**>3.0**	**Total**
<1year	2(11.1%)	3(16.7%)	5(27.8%)	8(44.4%)	18(23.7%)
1-5year	4(40%)	1(10%)	4(40%)	1(10%)	10(13.1%)
>5year	20(41.7%)	16(33.3%)	11(22.9%)	1(20.8%)	48(63.2%)

X^2=25.11, p<0.01

Table 3: UPCR vs Dengue Severity (WHO classification)

Dengue classification	**UPCR <0.5**	**0.5-1.0**	**1.0-3.0**	**>3**	**Total**
Category A	10(52.6%)	6(31.6%)	3(15.8%)	0	19(25%)
Category B	11(39.3%)	8(28.6%)	7(25%)	2(7.1%)	28(36.8%)
Category C	5(17.2%)	6(20.7%)	10(34.5%)	8(27.6%)	29(38.2%)

X^2=14.551, p = 0.024

Table 4: UPCR vs Ooutcome

Outcome	**<0.5**	**0.5-1.0**	**1.0-3.0**	**>3**	**Total**
Discharge	26(35.6%)	20(27.4%)	19(26.2%)	8(10.9%)	73(96%)
Death	0	0	1(33.3%)	2(66.7%)	3(4%)

X^2= 8.745, p= 0.033

Table 5: Significant Proteinuria vs Outcome

Proteinuria/ outcome	<100	100-300	>300	Total
Death	2 (66.6%)	1(33.3%)	0	3
Discharge	70 (95.9%)	2 (2.7%)	1 (1.4%)	73

X^2= 7.133, P = 0.028

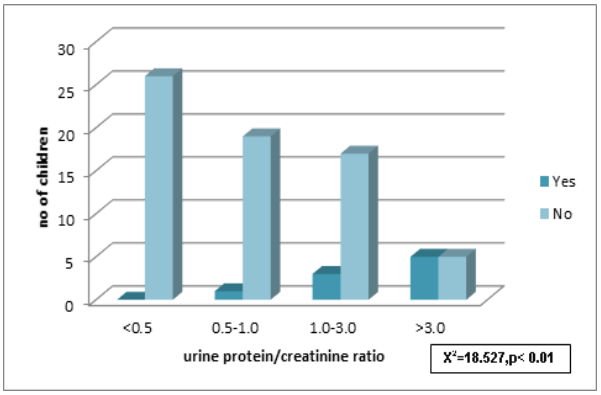

Fig. 1: UPCR vs Bleeding Manifestations

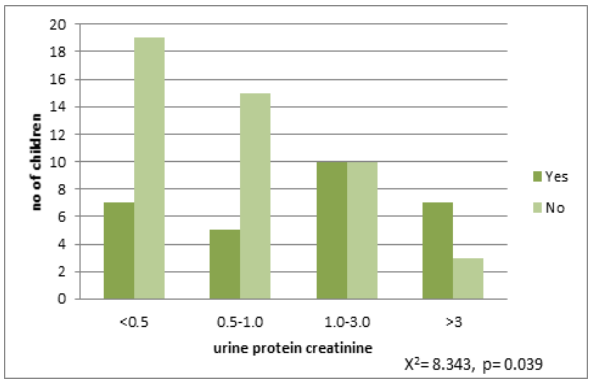

Fig. 2: UPCR vs Effusions

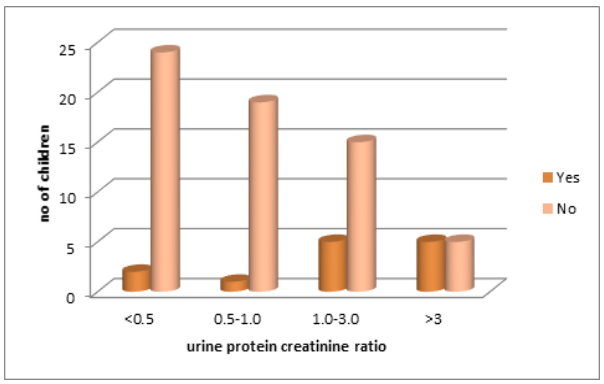

Fig. 3: UPCR vs Inotrope Usage

B. Proteinuria: 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 the study, 3 cases had proteinuria in range of 100-300mg/dl/day and only one case had severe proteinuria.

1. **Proteinuria Vs Severity of Dengue:** The association between proteinuria and severity of dengue was studied. All 19 children in category A (mild disease) did not have significant proteinuria (<100mg/dl). Only 7% of children with moderate disease severity had significant proteinuria. In severe disease, 7% had significant proteinuria. The association of proteinuria and severity of dengue studied did not reach levels of statistical significance (p >0.05).
2. **Proteinuria vs Outcome:** We studied the correlation of proteinuria and outcome (Table 5). In our series, 3 deaths occurred due to dengue, among which 2 children had proteinuria < 100mg/dl and 1 child had proteinuria >100mg/dl. The association was statistically significant. (p = 0.028)

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.

In our study out of a total of 76 children, 18 were infants, 10 were between 1-5 yrs and 48 children were above 5years of age. These findings are similar to the observation of Graham et al.[3] We did not find any difference in its incidence according to gender. However there are some reports of a higher incidence occurring in males.[4] Children were categorized into 3 groups, based on WHO classification. 19 (25%) children were grouped in category A, 28 (36.8%) children in Category B and category C contained 29 (38.2%) children.

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.[5] They performed serial proteinuria and correlated the peak proteinuria with day of illness.The association of severity of dengue and higher urine protein creatinine ratio was studied, it was statistically significant (p =0.024). 27.6% children in category C had urine protein creatinine ratio >3. 52.6% children with age group less than 1yr had UPCR <0.5. 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.[6-7] Lye who did a study on Predictive Value of Proteinuria in Adult Dengue Severity and concluded that Proteinuria measured by a laboratory-based UPCR

test may be sensitive and specific in prognosticating adult dengue patients.[8]

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. 34 children in our group required transfusion, in the form of fresh frozen plasma or platelets, depending on the clinical condition, among which 50% had UPCR>1. It had no statistical significance (p =0.255). 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 are available.[9-11]

In this study, we observed that there is a significant association for occurrence of third space collection and UPCR (p value= 0.039). 58.6% children with effusions had UPCR> 1. There was a positive correlation of UPCR and requirement of inotropic support in our study; we observed that 38.5% children with UPCR >3 required inotropes during hospital stay where as only 15.4% of children with UPCR<0.5 required inotropes. This observation reached levels of statistical significance(p = 0.007). In our study, 3 deaths occurred of which 2 children had UPCR > 3 and 1 had UPCR between 1-3. The association was statistically significant (p = 0.033). Some of the other studies in adult population too have established a positive correlation between the severity of disease and raised UPCR.[12-13] 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 shock syndrome.[14-15]

Conclusions

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 proteinuria estimation in all children afflicted with dengue fever as a screening device for hospitalization, management and prognostication.

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