Predictive Value of Proteinuria in Assessing Severity of Dengue Infection in Children

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Background: Dengue fever has emerged as a major health problem globally with several complications occur which lead to increasing morbidity and mortality. 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 pediatric population. This study was undertaken to establish early predictors of disease severity, urine protein-creatinine ratio (UPCR), and proteinuria in children with dengue. Objectives: The objectives of the study were to correlate UPCR with severity of illness in children diagnosed to have dengue infection. Materials and Methods: A hospital-based prospective observational study was carried out among 140 children admitted at Niloufer Hospital, a tertiary care teaching pediatric hospital attached to Osmania Medical College, Hyderabad, Telangana, during the study period of 2 years. SPSS 19.0 software was used to analyze the data. Results: Among the 140 children, 29 children were categorized as severe dengue, 34 as dengue with warning signs, and 77 as probable dengue. There were 11 deaths which counted for 0.07% of total study population. The mean UPCR and proteinuria showed peak during day 5 and day 6 of illness in all three groups of study population with statistical significance of $P < 0.05$. Conclusion: There was a positive correlation between UPCR and severity of dengue illness. The onset and the peak of proteinuria using UPCR have a significant association with subsequent development of severe dengue.

Key words: Dengue fever, dip stick, proteinuria, urine protein-creatinine ratio

INTRODUCTION

D engue is the most common mosquito borne endemic-epidemic arboviral infection in many tropical and subtropical regions of the world.[¹] The first dengue fever in India was reported during 1956 from Vellore and the first dengue hemorrhagic fever occurred in Calcutta in 1963.[²] An estimated 50–100 million dengue infections occur annually, approximately 2.5 million people live in dengue endemic countries.[³] Case fatality rates vary from 1% to 5% but can be <1% with appropriate treatment. In its most severe form, it manifests itself clinically as dengue hemorrhage fever and dengue manifestation, which may lead to circulatory collapse called dengue shock syndrome (DSS). Dengue fever in children is associated with many challenges as well as considerable mortality and morbidity. Dengue reinfection is observed to be more severe in children due to immunological phenomenon.[⁴]

The risk factors for the development of severe dengue are poorly characterized and consequently uncomplicated cases are frequently hospitalized during the critical phase for capillary leakage syndrome, thereby increasing the financial burden to the patients. Therefore, improvements in early diagnosis and risk predictions for severe disease are urgently needed.

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needed particularly with respect to identification of simple clinical and laboratory indicators that are practical and affordable for use in resource poor countries. Ideally, the test should be cheap, fast, easy to perform, and highly sensitive and specific. Nguyen-Pouplin et al.\textsuperscript{[5]} observed an increase in urinary protein clearance due to increased systemic vascular permeability that occurs in severe dengue. Subsequently, it has been proposed that a simple urine protein excretion screening test could be indicator of the severe form of dengue and therefore guide the triage and monitoring of the patients with suspected dengue infection.

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.\textsuperscript{[10]} Moreover, 24 h urinary albumin measurement is cumbersome and time consuming to perform. However, measurement of spot urinary protein estimation as well as urinary protein-creatinine ratio (UPCR) is a more practical and therefore readily acceptable alternative. 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 UPCR and significant proteinuria to predict the disease severity and outcome as well as enable in the management in pediatric patients with dengue infection.

**MATERIALS AND METHODS**

**Study Design**

This was a hospital-based prospective observational study.

**Study Setting**

The present study was conducted at Niloufer institute for women and children, a tertiary care teaching pediatric hospital attached to Osmania Medical College, Hyderabad, Telangana, India.

**Study Subjects**

Admitted children of age group 1 month–12 years diagnosed to have dengue infection.

**Sample Size**

A total of 140 children of age group 1 month–12 years diagnosed to have dengue infection during the study period of 2 years and fulfill inclusion and exclusion criteria of the study.

**Study Period**

The study period was from June 2017 to May 2019, that is, 2 years.

**Sampling Technique**

All 140 children who were admitted and had signs and symptoms of dengue fever during the study period and were also had positive for Ns1Ag and or dengue IgM were included in the study.

**Inclusion Criteria**

Children of age group 1 month–12 years diagnosed to have dengue infection admitted during the study period of 2 years.

**Exclusion Criteria**

Children with age <1 month and with preexisting renal disease who did not give consent are excluded from the study.

**Data Collection**

All the 140 patients who were admitted, who showed signs and symptoms of dengue fever, and were also had positive for Ns1Ag and or dengue IgM in the blood were included in the study. Day of onset of fever was noted. Daily early morning urine samples were collected and serial measurements of urine dip stick and urine protein-creatinine ratio (UPCR) were sent. Daily platelet counts were measured. Samples were collected from day 3 of fever to day 9 or discharge whichever comes earlier. Patients were categorized into severe dengue, dengue with warning signs, and probable dengue as per the WHO criteria.

**Data Analysis**

Data were entered into Microsoft Excel 2007 version and analyzed using SPSS 19.0 version.

**RESULTS**

Severe dengue is primarily a disease of infants and children, although adults may be afflicted with severe disease. Among the 140 children, 29 children were categorized as severe dengue, 34 as dengue with warning signs, and 77 as probable dengue. The mean age of presentation of probable dengue was 6.43 years, dengue with warning signs was 6.56 years, and severe dengue was 6.79 years. Out of 140 study subjects, 62% are male and 38% are female. The incidence of severe dengue is slightly more in males compared to females, which was not of statistical significance. There were 11 deaths in the study which counted for 0.07% of total study population. The incidence of severe dengue was 20.7%, which is much higher than its natural incidence and 7.8% of total cases died which accounts for 38% of severe dengue cases. The mean urine dipstick values showed increasing trend till day 5 and day 6 of fever followed by decreasing trend with higher values in severe dengue compared to other groups with statistically significant, as shown in Table 1.
It was seen from Graph 1 that the UPCR in severe dengue showed peak on day 5 and day 6 with mean values of 3.57 and 3.54, respectively ($P = 0.001$).

It was observed from Table 2 that dipstick showed the peak on day 5 and day 6 with mean values of 3.89 and 3.78, respectively. The mean dipstick and UPCR showed higher values when compared to other groups which were statistically significant, $P < 0.05$. The mean UPCR and dipstick values were in a lower range in probable dengue and dengue with warning signs, indicating increasing in proteinuria as the severity of dengue increases.

The mean platelet count values showed increasing trend till day 5 and day 6 of fever followed by changing patterns which was statistically insignificant, as seen in Graph 2.

DISCUSSION

The mean age of the study population was 6.59. The mean age of dengue with warning signs was 6.56 years. Similar finding observed in Andries et al.[7] study it was 8.5 years. The mean age of presentation of severe dengue was 6.79 years. In our study, 28.5% were <5 years, 50.7% were between 6 and 10 years, and 20.7% were between 11 and 12 years, compared to the study done by Datla et al.[8] In our study, 87 (62%) were male and 53 (38%) were female. The incidence of dengue among males was more in males than females which was same in cases of Wichmann et al.[4] in which 45 (59%) were male and 31 (41%) were female. In our study, in probable dengue group, 67.5% were male, and in warning signs group, 58.8% were male. Similar findings were observed in Andries et al.[7] and Datla et al.[8] study where 62.5% and 51.7%, respectively.

In our study, probable dengue mean urine dip stick protein value on day 3 of fever was 0.32, then showing an increasing trend with highest value on day 4 was 1.24 followed by a decreasing trend from day 5 to day 9. In dengue with warning signs, the mean value on day 3 was 1.41, which is higher than in probable dengue, followed by increasing trend with highest value on day 5 and 6 was 2.2 and 2.7, respectively. In severe dengue, the mean value on day 3 was 2.11 with highest value on day 6 was 3.38. A study by Andries et al.[7] observed proteinuria in 75% of severe dengue infection patients, in which urine dipstick for proteins was positive in 52% of dengue with warning signs patients and 38% of dengue without warning signs. A study done by Sultana et al., out of 361 subjects, 4.4% of patients were found to have proteinuria.[9] Another study by Wills et al. demonstrated among children with DSS markedly reduced plasma concentrations of different sized proteins with a corresponding increase in fractional urinary clearances of the same proteins.[10] A study done by Lumpaopong et al.

<table>
<thead>
<tr>
<th>Urine dip stick values</th>
<th>Probable dengue mean</th>
<th>S.D.</th>
<th>Dengue with warning signs</th>
<th>S.D.</th>
<th>Severe dengue</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>0.32</td>
<td>0.02</td>
<td>1.41</td>
<td>0.32</td>
<td>2.11</td>
<td>0.62</td>
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<td>Day 4</td>
<td>1.24</td>
<td>0.16</td>
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<td>2.77</td>
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<td>Day 5</td>
<td>1.15</td>
<td>0.12</td>
<td>2.2</td>
<td>0.23</td>
<td>3.29</td>
<td>1.0</td>
</tr>
<tr>
<td>Day 6</td>
<td>1.02</td>
<td>0.09</td>
<td>2.2</td>
<td>0.43</td>
<td>3.38</td>
<td>1.13</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.00</td>
<td>0.03</td>
<td>1.62</td>
<td>0.12</td>
<td>2.52</td>
<td>0.98</td>
</tr>
<tr>
<td>Day 8</td>
<td>0.87</td>
<td>0.37</td>
<td>1.33</td>
<td>0.09</td>
<td>1.82</td>
<td>0.74</td>
</tr>
<tr>
<td>Day 9</td>
<td>0.60</td>
<td>0.22</td>
<td>1.04</td>
<td>0.32</td>
<td>1.5</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Graph 1: Mean urine protein-creatinine ratio values from day 3 to day 9 in dengue cases
found that proteinuria in 15% of children with dengue fever compared to 27% of those with dengue hemorrhagic fever.[11]

In our study, daily UPCR was measured and compared between the three groups over a period of 7 days. In probable dengue group, mean value of UPCR was 0.14 on day 3. Then it showed increasing trend till day 5 (mean UPCR=0.24) and followed decreasing trend till day 9 (UPCR=0.10). In dengue with warning signs group, the mean value on day 3 was 0.58 followed by highest value on day 6 was 1.97 followed by decreasing trend till day 9. In severe group, the mean values compared to other two groups were higher on all days with highest value of 3.95 on day 6 of illness. Similar results were observed in a study done by García et al.[12] which showed that 27.6% in severe dengue group showed that UPCR was more than 3. Multivariate analysis of UPCR during the course of the disease indicated that this ratio was significantly higher 6–7 days after the onset of fever which was in agreement with the study conducted by Andries et al.[7] Similarly, a retrospective study done by Phakhounthong et al.[13] in Cambodia also revealed that the five indicators for dengue severity included hematocrit, Glasgow Coma Scale, urine protein, creatinine, and platelet count.

CONCLUSION

Our study showed that there was a significant association between proteinuria and severity of dengue infection. UPCR was also high on day 5 and 6 of dengue fever which coincides with the stage of critical period, then showing a decreasing trend with coincides with the recovery phase of illness. Urine dip stick for proteins and UPCR could be used for triaging the patients at hospital admission and for anticipating the course of illness. Urine dip stick being easily available and simple to measure can be used in peripheral set ups like PHCs who first come in contact with the patient, for triaging and early referral of patients requiring higher level of care.

Limitations

Renal function is not routinely assessed in hospitalized for suspected or confirmed dengue cases. There is a need for a future study to assess simultaneously the various parameters associated with a renal dysfunction such as electrolyte disturbances, dehydration status, GFR, and renal biopsies. We were not able to explore potential confounding factors for proteinuria, primary viral infections such as adenovirus or concomitant enterovirus, and non-dengue virus infections.

RECOMMENDATIONS

Standardization of UPCR values in dengue infection as per severity for triage of patients is necessary and Usage of dipstick for proteins at peripheral centres is needed for early referral.

REFERENCES