e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(10); 565-569

Original Research Article

A Study to Assess the Correlation of Proteinuria and Urine Protein/ Creatinine Ratio with Disease Severity in Pediatric Dengue Fever

Ajit Kumar Singh[1], Sachin Kumar[2], Nagendra Prasad Gupta[3]

[1]Senior Resident, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

[2]Senior Resident, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

[3]Professor, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

Received: 14-07-2023 Revised: 21-08-2023 / Accepted: 25-09-2023

Corresponding Author: Dr. Sachin Kumar

Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the correlation of proteinuria and urine protein/creatinine ratio with disease severity in pediatric dengue fever.

Methods: The present study was a hospital based, serially enrolled, prospective one which was carried out at Department of Pediatrics for the period of 1 year. A total of 200 children met the inclusion criteria. Children aged 1 month to 18years, hospitalized with clinical features of dengue and testing positive serology (NS1, IgM) were included in the study.

Results: Of these 42 were infants, 30 between 1-8 years and 60 children were above 8 years of age of which 150 were boys and 50 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. 20 children had bleeding manifestations during course of illness, among which 10 had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations ($p<0.05$). In this study, 180 children had third space collections. In this study, 25% children required inotropes. It was observed that cases who needed inotropes had higher UPCR and this association was statistically significant. The final outcome was noted as discharged or death in each group. We had 10 deaths in our study, in which 6 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 and was statistically significant. The proteinuria in urine sample was quantified by pyrogallol test, the laboratory standard value of which was 100mg/dl.

Conclusion: 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.

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

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 presence of microalbuminuria has been postulated as potential risk predictor for severe dengue [4,5], but there is little information on the magnitude, timing of onset, or evolution of urinary protein excretion during infection. Also 24-hour urinary albumin measurements are time consuming to perform. Both measurement of spot urine protein estimation as well as urine protein to creatinine ratio is a less cumbersome and are more practical method. Measurement of spot urine protein to creatinine ratio is much easier approach and hence acceptable method. [6] The spot PCR is obtained by the ratio between urine protein excretion (measured by 24-hour protein excretion or spot urine sample) and creatinine excretion, expressed as mg/mmol or mg/mmol. Spot PCR represents a practical alternative to the 24-hour urine collection because it is easier to obtain and is not influenced by variations in water intake or diuresis. [6]

The aim of the present study was to assess the correlation of proteinuria and urine protein/creatinine ratio with disease severity in pediatric dengue fever.

Materials and Methods

The present study was a hospital based, serially enrolled, prospective one which was carried out at Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India for the period of 1 year. A total of 200 children met the inclusion criteria. 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.

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.

Statistical Analysis

The recorded data was compiled and entered in a spread sheet 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

Table 1: Age vs UPRC Distribution

Age/UPCR	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
<1year	4	8	14	16	42
1-8year	25	5	26	4	60
>8year	46	35	15	2	98
Total	75 (37.5)	48 (24)	55 (27.5)	22 (11)	200 (100)

Of these 42 were infants, 30 between 1-8 years and 60 children were above 8 years of age of which 150 were boys and 50 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.

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	4	6	10	20
No	75	40	45	20	180

20 children had bleeding manifestations during course of illness, among which 10 had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations ($p<0.05$). In this study, 180 children had third space collections.

Table 3: UPCR vs Inotrope Usage

Inotropes	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
Yes	10	5	20	15	50
No	65	43	35	7	150
Total	75 (37.5)	48 (24)	55 (27.5)	22 (11)	200 (100)

In this study, 25% children required inotropes. It was observed that cases who needed inotropes had higher UPCR and this association was statistically significant.

Table 4: UPCR vs Outcome

Outcome	<0.5	0.5-1.0	1.0-3.0	>3	Total
Discharge	75	45	50	20	190
Death	0	0	4	6	10

The final outcome was noted as discharged or death in each group. We had 10 deaths in our study, in which 6 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 and was statistically significant.

Table 5: Significant Proteinuria vs Outcome

Proteinuria/ outcome	<100	100-300	>300	Total
Death	6	4	0	10
Discharge	165	15	10	190

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, 10 deaths occurred due to dengue, among which 6 children had proteinuria < 100mg/dl and 2 child had proteinuria >100mg/dl. The association was statistically significant.

Discussion

Dengue is one of the most important emerging viral disease of humans in the world afflicting humanity in terms of morbidity and mortality. Dengue mainly affects the pediatric age group and mortality due to dengue is due to capillary permeability, abnormalities of hemostasis, and in severe cases, dengue shock syndrome. [7] 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.

Of these 42 were infants, 30 between 1-8 years and 60 children were above 8 years of age of which 150 were boys and 50 girls. These findings are similar to the observation of Graham et al. [8] We did not find any difference in its incidence according to gender. However there are some reports of a higher incidence occurring in males. [9] 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. 20 children had bleeding manifestations during course of illness, among which 10 had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations ($p<0.05$). In this study, 180 children had third space collections. In this study, 25% children required inotropes. It was observed that cases who needed inotropes had higher UPCR and this association was statistically significant. Our findings were consistent with those of Yip WC [10] and Vasanwala FF [11] 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. [12] 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. [13-15]

The final outcome was noted as discharged or death in each group. We had 10 deaths in our study, in which 6 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 and was statistically significant. 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, 10 deaths occurred due to dengue, among which 6 children had proteinuria < 100mg/dl and 2 child had proteinuria >100mg/dl. The association was statistically significant. 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. [3,16]

Conclusion

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.

References

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. PLoS Negl 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 Organi - zation; 2009.
3. Wills BA, Oragui EE, Dung NM, Loan HT, Chau NV, Farrar JJ, Levin M. Size and charge characteristics of the protein leak in dengue shock syndrome. Journal of Infectious Diseases. 2004 Aug 15;190(4):810-8.
4. Chen Y, Maguire T, Hileman RE, Fromm JR, Esko JD, Linhardt RJ, Marks RM. Dengue virus infectivity depends on envelope protein binding to target cell heparan sulfate. Nature medicine. 1997 Aug 1;3(8):866-71.
5. Lumpaopong A, Kaewplang P, Watanave - eradej V, Thirakhupt P, Chamnanvanakij S, Srisuwan K, Pongwilairat N, Chulamokha Y. Electrolyte disturbances and abnormal urine analysis in children with dengue infection. Southeast Asian journal of tropical medicine and public health. 2010 Jan 1;41(1):72.
6. Bakker AJ. Detection of microalbuminuria: Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio aver albumin concentration. Diabetes care. 1999 Feb 1;22(2):307.
7. National Guidelines for Clinical Management of Dengue Fever; 2015.
8. Graham RR, Juffrie M, Tan R, Hayes CG, Laksono I, Ma'Roef C, Porter KR, Halstead SB. A prospective seroepidemiologic study on dengue in children four to nine years of age in Yogyakarta, Indonesia I. studies in 1995-1996. The American journal of tropical medicine and hygiene. 1999 Sep 1;61(3):412-9.
9. Wali JP, Biswas A, Handa R, Aggarwal P, Wig N, Dwivedi SN. Dengue haemorrhagic fever in adults: a prospective study of 110 cases. Tropical doctor. 1999 Jan;29(1):27-30.
10. Yip WC. Dengue haemorrhagic fever: current approaches to management. Medical Progress. 1980 Oct;7(13):201-9.
11. Vasanwala FF, Puvanendran R, Ng JM, Suhail SM. Two cases of self-limiting nephropathies secondary to dengue haemorrhagic fever. Singapore Med J. 2009 Jul 1;50(7):e253-5.
12. Vasanwala FF, Puvanendran R, Fook-Chong S, Ng JM, Suhail SM, Lee KH. Could peak proteinuria determine whether patient with dengue fever develop dengue hemorrhagic/ dengue shock syndrome?-A prospective cohort study. BMC Infectious Diseases. 2011 Dec; 11:1-6.
13. Lum LC, Goh AY, Chan PW, El-Amin AL, Lam SK. Risk factors for hemorrhage in severe dengue infections. The Journal of pediatrics. 2002 May 1;140(5):629-31.
14. Wills BA, Oragui EE, Stephens AC, Daramola OA, Dung NM, Loan HT, Chau NV, Chambers M, Stepniewska K, Farrar JJ, Levin M. Coagulation abnormalities in dengue hemorrhagic fever: serial investigations in 167 Vietnamese children with dengue shock

syndrome. Clinical infectious diseases. 2002 Aug 1;35(3):277-85.
15. Rigau-Pérez JG et al., Dengue and dengue haemorrhagic fever. Lancet,1998,352:971-77.
16. Lumpaopong A, Kaewplang P, Watanavee - radej V, Thirakhupt P, Chamnanvanakij S, Srisuwan K, Pongwilairat N, Chulamokha Y. Electrolyte disturbances and abnormal urine analysis in children with dengue infection. Southeast Asian journal of tropical medicine and public health. 2010 Jan 1;41(1):72.