Acute Renal Failure in Dengue Infection

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ABSTRACT

Introduction: Acute Renal Failure (RF) is a rare but well recognized complication of Dengue Infection (DI). There has been paucity of published data regarding renal involvement in DI.

Aim: The aim of the present study was to elucidate different clinical presentations, disease outcomes of DI. To study the frequency, severity and predictors of RF in DI.

Materials and Methods: Patients diagnosed either as Dengue Fever (DF) or Dengue Haemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) respectively were enrolled for this study. The diagnostic criteria for DI were febrile illness associated with one of the following: 1) detection of dengue-specific IgM capture antibody or Non-Structural Protein1 (NS1) antigen; or 2) a four-fold or greater increase of dengue-specific IgG capture antibody by ELISA and haemoagglutination inhibition assay. Patients were diagnosed as having Acute RF, if serum creatinine was >1.2 mg/dl or who showed improvement by 50% in serum creatinine from the initial value. It is an observational study of medical charts, data of age, gender, and medical history of any underlying diseases in association with the severity of DI of each patient recorded. All of the laboratory results were collected. Parameters that influenced the clinical presentations and outcomes for development of classical DF or DHF/DSS in patients with or without RF were analysed and compared. Descriptive and inferential statistical analysis was carried. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used.

Results: Most common symptoms were fever followed by headache and pain in abdomen. Among the patients with RF, all patients had recovery. The patients with DHF/DSS were more susceptible to develop renal failure compared to DF group. There were statistically significant higher frequencies of renal failure, haemoconcentration, thrombocytopenia, low serum cholesterol. Patients in the RF group also had significantly higher percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol compared to non-RF group. There were no mortality and none of them had to receive renal replacement therapy during hospitalization.

Conclusion: Patients with DHF/DSS were more susceptible to develop renal failure compared to DF group. Patients in the RF group had higher percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol.

Keywords: Cholesterol, Fever, Headache, Renal replacement therapy, Thrombocytopenia

INTRODUCTION

Dengue infection (DI) is a tropical illness caused by Dengue virus [1]. The incidence of DI is increasing at estimate of 50 to 100 million cases per annum worldwide [2]. The presentation of DI can be a classical Dengue Fever (DF) or Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS) [2]. Acute RF is a rare but well-recognized complication of DI, with an incidence which varies from 0.3% to 3.3% in different populations [3]. The presence of comorbid illness like diabetes mellitus, hypertension can have impact on prognosis of DI [2]. To our knowledge, there has been paucity of published data regarding renal involvement in DI. The aim of this study was to elucidate about different clinical presentations, disease outcomes of dengue viral infection and to study the frequency, severity and predictors of RF in DI.

MATERIALS AND METHODS

Participants and Definitions: From January 2013 to January 2015, 101 patients diagnosed either as DF or DHF/DSS at Vydehi Hospital were enrolled for this study from the total of 139 DI patients after satisfying inclusion/exclusion criteria. The diagnostic criteria for DI were febrile illness associated with one of the following laboratory confirmation tests: 1) detection of dengue specific IgM capture antibody or NS1 antigen; or (2) a four-fold or greater increase of dengue-specific IgG capture antibody by ELISA and haemoagglutination inhibition assay in paired serum samples.

Cases with only a single positive dengue IgG result or without detailed history were excluded. Patients with no serum creatinine data at admission or with incomplete demographic data were excluded.

According to the criteria from the World Health Organization (WHO), patients who have DF and haemorrhagic manifestations, low platelet count, and objective evidence of leaky capillaries (≥20% elevation in haematocrit, lower serum albumin, and pleural or other effusions) were classified as having DHF (WHO classification, DHF grades I/II). Those with evidence of circulatory failure (pulse pressure ≤20 mmHg, hypotension, or frank shock) were classified as having DSS (WHO classification, DHF grades III/IV) [2]. Patients were diagnosed as having Acute RF, if serum creatinine was >1.2 mg/dl or who showed improvement by 50% on follow up from initial serum creatinine [4,5].

Study Design: It is an observational study of medical charts, demographic data of age, gender, and medical history of any underlying diseases in association with the severity of dengue infection of each patient recorded. All of the laboratory results at first hospital visit were collected for statistical analyses. The recording of underlying chronic diseases like hypertension, diabetes mellitus was done. Proteinuria was defined as urinary protein appearing ≥1+ (30mg/dl) by dipstick test [6], and microscopic haematuria was defined as >5RBC/HPF [7]. Parameters that possibly influenced the clinical presentations and outcomes for development of classical DF or DHF/

DSS in patients with or without RF were analysed and compared.

Study hypothesis was based on: a) varying clinical presentations, disease outcomes of DI; b) higher incidence of bleeding tendency, shock, proteinuria, haemoconcentration, thrombocytopenia, low serum cholesterol in RF group in DI; and c) higher incidence of bleeding tendency, shock, proteinuria, RF, haemoconcentration, thrombocytopenia, low serum cholesterol in more severe forms of DI like DHF/DSS.

STATISTICAL ANALYSIS

Descriptive statistical analysis was done for parameters like raised transaminases, raised LDH level and inferential statistical analysis was done for parameters like incidence of bleeding tendency, shock, proteinuria and RF, haemoconcentration, thrombocytopenia, low serum cholesterol, where statistically significant p-value was found. Results on continuous measurements were presented on Mean±SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5% level of significance. The following assumptions on data are made, Assumptions: 1) Dependent variables should be normally distributed; 2) Samples drawn from the population should be random, and cases of the samples should be independent [8-10]. Analysis of Variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients, Student t-test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/Fisher-Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (p-value: 0.05<p<0.10)

* Moderately significant (p-value: 0.01<p£ 0.05)

** Strongly significant (p-value: p£0.01)

Statistical Software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft word and Excel were used to generate graphs, tables etc.

RESULTS

Among 101 patients with confirmed DI, 74 (73.3%) were men and 27(26.7%) were women with a mean age of 31.62±12.62 years. A total of 70 (70.2%) patients had classical DF, and 31(29.2%) patients had DHF/DSS. RF group with 16 (15.8%) patients was defined as serum creatinine of >1.2mg%. Most common symptoms were fever (100%) followed by headache (82%) and pain in abdomen (75%). Statistically significant (p<0.001) bleeding tendency, shock, proteinuria and RF [Table/Fig-1] were present more in DHF/DSS than in DF. Analysis by Fisher-exact test revealed that the DF group had no significant presence of hypertension, diabetes compared with the DHF/DSS group (strongly significant was if p≤0.01). The time from the onset of fever to the detection of fever in DF, DHS and DSS groups did not show a significant difference (4.41±1.62 days versus 3.73±1.56 days versus 4.58±2.54 days) with p=0.275 on analysis of variance (ANOVA) test, checked at 5% level of significance (strongly significant was if p≤0.01). Among the 16 patients with RF, all patients had recovery from renal failure. The differences in clinical presentations of DF and DHF/DSS are shown in [Table/Fig-2]. The patients with DHF/DSS were more susceptible to develop renal failure compared to DF group (62% versus 38%). There were statistically significant higher frequencies of renal failure, haemoconcentration, thrombocytopenia, low serum cholesterol in DHF/DSS group. Raised transaminases, raised LDH level were noted in the DHF/DSS group compared with DF, however, there was no significant difference in frequency of other mentioned symptoms/

	DF (n=70)	DHF (n=19)	DSS (n=12)	Total (n=101)	p-value
Bleeding	0(0%)	19(100%)	6(50%)	25(24.8%)	<0.001**
Renal failure (RF)	1(1.4%)	4(21.1%)	11(91.7%)	16(15.8%)	<0.001**
Shock	2(2.9%)	2(10.5%)	12(100%)	16(15.8%)	<0.001**
Haematuria	2(2.9%)	1(5.3%)	2(16.7%)	5(5%)	0.104
Proteinuria	4(5.7%)	4(21.1%)	4(33.3%)	12(11.9%)	0.008**

[Table/Fig-1]: Comparison of frequency of variables like bleeding/renal failure/shock/haematuria/proteinuria in different groups of patients studied.
Chi-Square test/Fisher-exact test

Variables	DF	DHF	DSS	Total	p-value
Urea (mg%)	29.44±9.41	35.92±18.34	53.53±8.96	33.52±13.83	<0.001**
Creatinine mg% (Day1)	0.88±0.23	1.04±0.39	1.52±0.30	0.99±0.34	<0.001**
Creatinine mg% (Day 14)	0.66±0.19	0.65±0.22	0.88±0.19	0.69±0.20	0.001**
Haematocrit (%)	44.16±6.43	46.93±3.62	47.71±7.89	45.10±6.31	0.073+
Haemoglobin (g/dl)	13.91±2.18	15.13±1.34	14.97±2.75	14.26±2.17	0.045*
Platelets (cells/cmm)	83754.29±71560.12	47815.79±39127	24258.33±20133.67	69924.75±65806.89	0.003**
Creatine kinase (U/L)	122.14±219.87	140.79±145.73	100.83±132.75	123.12±198.08	0.861
Total Bilirubin (mg/dl)	1.15±1.08	0.97±0.72	1.99±2.85	1.22±1.37	0.101
Direct Bilirubin (mg/dl)	0.45±0.61	0.47±0.51	0.75±0.83	0.49±0.63	0.307
Albumin (g/l)	3.33±0.77	3.55±0.97	3.37±0.53	3.38±0.78	0.559
AST (U/l)	164.73±240.87	349.79±1102.96	891.00±2502.45	285.83±1001.42	0.063+
ALT (U/l)	94.90±148.80	125.37±201.66	331.83±803.51	128.78±315.23	0.054+
ALP (U/l)	105.81±65.20	94.00±39.04	83.67±39.47	100.96±58.65	0.413
Lactate Dehydrogenase (U/L)	85.49±63.85	304.95±854.41	164.50±124.14	136.16±378.44	0.077+
Sodium (mmol/L)	135.64±16.59	136.96±4.08	135.05±1.91	135.82±13.92	0.917
Potassium (mmol/L)	11.31±45.37	4.15±0.43	4.22±0.58	9.12±37.84	0.686
Cholesterol (mg/dl)	141.59±36.45	159.96±28.26	120.58±45.49	142.55±37.47	0.015*
Total Leucocyte count (cells/cmm)	11048.64±19180.19	7668.42±10572.5	18691.67±29127.82	11320.84±19400.78	0.301
Prothrombin time	12.24±2.20	12.53±1.27	12.95±3.11	12.38±2.18	0.555
Activated partial thromboplastin time (seconds)	31.63±8.67	31.29±10.74	31.11±7.33	31.50±8.87	0.977

[Table/Fig-2]: Comparison of mean of clinical variables in relation to different groups of patients studied.
ANOVA test

	Renal failure (RF)		All patients (n=101)	p-value
	Absent (n=85)	Present (n=16)		
Pulse (per minute)	85.31±11.82	87.00±11.91	85.57±11.79	0.600
SBP (mm Hg)	111.79±11.46	93.13±9.69	108.83±13.09	<0.001**
DBP (mm Hg)	73.04±7.41	66.63±10.60	72.02±8.27	0.004**
Respiratory Rate (per minute)	17.33±5.04	17.31±3.53	17.33±4.82	0.990
Temp (°F)	99.57±1.12	100.12±1.35	99.66±1.17	0.086+

[Table/Fig-3]: Comparison of vitals in relation to renal failure status of patients studied.
Student t-test

Variables	Renal failure (RF)		All patients (n=101)	p-value
	Absent (n=85)	Present (n=16)		
Urea (mg%)	28.98±8.91	57.64±9.69	33.52±13.83	<0.001**
Creatinine mg% (Day1)	0.87±0.21	1.59±0.29	0.99±0.34	<0.001**
Creatinine mg% (Day 14)	0.64±0.18	0.93±0.11	0.69±0.20	<0.001**
Haematocrit (%)	44.64±6.18	47.58±6.62	45.10±6.31	0.088+
Hemoglobin (g/dl)	14.06±2.10	15.34±2.32	14.26±2.17	0.030*
Platelets (cells/cmm)	77832.94±68221.56	27912.50±23870.68	69924.75±65806.89	0.005**
Creatine kinase (U/L)	127.59±210.53	99.38±112.46	123.12±198.08	0.604
Total Bilirubin (mg/dl)	1.10±1.02	1.82±2.49	1.22±1.37	0.053+
Direct Bilirubin (mg/dl)	0.45±0.58	0.74±0.79	0.49±0.63	0.086+
Albumin (g/l)	3.40±0.82	3.28±0.54	3.38±0.78	0.590
AST (U/l)	207.73±560.37	700.75±2170.00	285.83±1001.42	0.071+
ALT (U/l)	101.75±164.5	272.38±696.27	128.78±315.23	0.046
ALP (U/l)	103.27±61.75	88.69±37.28	100.96±58.65	0.364
Lactate Dehydrogenase (U/L)	134.86±409.94	143.06±116.73	136.16±378.44	0.937
Sodium (mmol/L)	135.90±15.13	135.37±3.13	135.82±13.92	0.889
Potassium (mmol/L)	10.04±41.22	4.22±0.51	9.12±37.84	0.575
Cholesterol (mg/dl)	145.57±34.00	126.50±50.62	142.55±37.47	0.062+
Total Leucocyte count (cells/cmm)	9943.59±17565.66	18637.50±26711.89	11320.84±19400.78	0.100
Prothrombin time	12.22±2.03	13.22±2.76	12.38±2.18	0.090+
Activated partial thromboplastin time (seconds)	31.82±9.08	29.83±7.66	31.50±8.87	0.414

[Table/Fig-4]: Blood investigations in relation to Renal failure status of patients studied.
Student t-test

no bleeding or hypotension is not clear. Whether the virus causes direct damage by invasion of the kidneys is not known [1]. Gender distribution showed male domination in this study to suffer from AKI. The male gender susceptibility could be related to more males working outside the house exposing them to greater risk of mosquito bite or whether social cause like better medical facility to males in this part of world, as mentioned in other studies [12,13]. In our study, the patients with DHF/DSS were more susceptible to develop RF compared to DF group due to hypotension, bleeding and shock like in other study [12]. In our study, there were statistically significant higher frequencies of RF, haemoconcentration, thrombocytopenia, low serum cholesterol in DHF/DSS group than DF as in other study [2]. In our study, patients in the RF group had significantly higher

signs and parameters like serum bilirubin, serum electrolytes, prothrombin time, APTT between DF and DHF/DSS in the patients with RF. Patients in the RF group also had significantly higher percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol [Tables/Fig-3,4]. There were no mortality and none of them had to receive renal replacement therapy during hospitalization.

DISCUSSION

Classic DF often presents as a self-limiting febrile illness, whereas DHF and DSS have high mortality [1]. Dengue infection has been associated with a variety of renal disorders [11]. Significant proteinuria of 74% was seen in severe DI. Similar to our study, haematuria has been noted in up to 12.5% in DI [1,11]. Unlike in other reported studies, incidence of Acute Kidney Injury was found to be higher in our study [11,12]. When RF complicates DI, it is almost always due to extensive capillary leak, hypotension, rhabdomyolysis, haemolysis and severe disseminated intravascular coagulation, which lead to hypoxia/ischemia and multiple organ dysfunction as reported in various case report studies [11,12]. In some patients, acute tubular necrosis is associated with interstitial oedema and mononuclear cell infiltration may lead to RF [1]. The exact mechanism of renal involvement in patients with DF who have

percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol like in other studies [12,14,15]. Unusual features in DF like hepatic, cardiac and nervous system involvement in DF has poor prognosis. Liver dysfunction manifests by the elevation of transaminases representing reactive hepatitis. Elevated transaminases in DF may be due to use of hepatotoxic drugs and direct attack of virus itself. There is hepatic inflammation leading to transaminitis in DF [14]. The mainstay of management of dengue fever is to give fluids to maintain adequate circulation while being careful not to deliver more than is absolutely necessary–a very delicate balancing act to prevent fluid overload [4,15].

LIMITATION

This study is one hospital-based design with the disadvantage of limited case number and the advantage of reducing bias on the factor of difference in medical care quality. Patients were only followed up until discharge and there was a lack of long-term follow-up.

CONCLUSION

Patients with DHF/DSS were more susceptible to develop renal failure compared to DF group. Patients in the RF group had higher percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol.

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