An Observational Study to Assess Renal Involvement in Dengue Fever Patients a Tertiary Care Hospital of Bangladesh

Moharam Ali[1], Milton Barua[2], Syedul Alam Kuryshi[3], Purna Jiban Chakma[4], Parvin Aktar[5], Nazim Uddin[6]

Author information:
1. MBBS, MD, Resident, Dept. of Neurology, CMCH, Chittagong
2. Senior consultant (Medicine), Sadar Hospital, Khagrachari
3. Senior consultant (Cardiology), Sadar hospital, khagrachari
4. RMO, Sadar Hospital, Khagrachhari,
5. Lecturer, Dept. of Biochemistry, CMC, Chittagong
6. Assistant Professor, Dept. of Medicine, Central Medical College, Cumilla

Address of correspondence: Dr. Milton Barua
MBBS, FCPS (Medicine), MD (Endocrinology), MRCP (Paces, UK)
Senior Consultant, Sadar Hospital, Khagrachori, dr.miltonbarua@gmail.com

ABSTRACT
Dengue virus infection may manifest clinically as undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Renal injury has been reported in dengue patients. Aim: To evaluate the renal involvement in dengue fever. Methods: 100 patients of dengue were evaluated who were admitted in Chittagong medical college hospital. Socio demographic, clinical biochemical and serological analysis were done. Results were analyzed by SPSS and p value considered significant when it was <0.05. Results: Among the 100 patients of dengue urine albumin was found among 55% of patients, urine RBC was found in 31% of patients, urine pus cell was found in 3% patients and urine cast was found in 6% of patients, blood urea was 35 ± 10.663 mg/dl and serum creatinine 1.39 ± 0.307 mg/dl. Among the 100 patients 82% patients improved, 11% patients were referred to different wards, 5% patients refused present hospital treatment and 2% patient died. Among the 82 improved patients mean $\pm$ SD of blood urea was 22.99 ± 8.085 mg/dl and creatinine was $1.359 \pm .283$ mg/dl. Patients who were referred and died also had mean $\pm$ SD of serum creatinine were 1.35 ± 0.212 mg/dl and 1.6 ± 0.404 mg/dl and mean $\pm$ SD urea were 38.45 ± 13.14 mg/dl and 50 ± 14.24 mg/dl respectively. Regarding analysis of renal involvement, >40mg/dl urea was found among 35(35%) patients whereas serum creatinine was found >1.2mg/dl among 27(27%) of patients and <3gm/dl serum albumin was found among 7(7%). Azotemia was associated with high level of mortality which was statistically significant (p<0.05). Conclusion: Dengue is a common viral disease in this area and renal involvement is also a common findings among the patients of dengue.

Key words: Haemorrahgic, DSS, Azotemia,

Introduction:

Dengue fever (DF) is currently the most important human viral mosquito-borne infection of public health significance, with millions of infections each year. The main dengue vector is the female of the *Aedes aegypti* mosquito. There are four serotypes of the dengue virus (DEN-1–DEN-4), a RNA flavivirus. They are antigenically closely related, but whereas infection with one serotype produces lifelong immunity to that serotype, immunity to other serotypes lasts only a few months[1,2].

Dengue virus infection may manifest clinically as undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS).[3] The classical form of dengue is an acute and self-limited disease characterized by fever, prostration, headaches, retro-orbital pain, myalgia, nausea, vomiting, skin rash, leukopenia and thrombocytopenia[4,5,6,7].More than 2.5 billion people are at risk of infections in over 200 countries worldwide. There are probably tens of millions of cases of dengue each year and at least five hundred thousand cases of DHF with mortality of about five percent in most countries.
The classical form of dengue has been known for more than a century in tropical south-East Asia and the Western Pacific region. Dengue haemorrhagic fever (DHF) was reported for the first time in Thailand in 1958[8], in Myanmar in 1970[9] and in India in 1963[10] with regular epidemics and endemicity. These countries geographically surround Bangladessh. On the other hand, Bangladesh is a country where most infectious diseases are prevailing. Of these, vector-borne diseases such as malaria, filariasis and kala-azar are endemic. Dengue is a similar vector-borne disease transmitted by Aedes aegypti. All favorable environmental conditions conducive for maintaining such mosquitoes are present here. In clinical practice many febrile infectious cases with features similar to dengue are found without any evidence of bacterial/ etiological agent by available tests. In 1964, there was an outbreak of dengue called 'Dhaka fever', which was the first documented outbreak of dengue infection in Bangladesh[11] and only one serotype DEN-3 was incriminated. This followed an outbreak in Kolkata (India) in 1963. A few cases of dengue fever were found in 1977-78 in selected areas of Bangladesh by a serological survey done by the Institute of Epidemiological Diseases Research (IEDCR). Some other sporadic studies undertaken with the help of WHO detected evidence of dengue in Dhaka city in the Seventies and Eighties. But no formal documentation was done and, up to 1986, it was thought that four major cities of Bangladesh were free of dengue haemorrhagic fever.[12] But over the last decade the scenario has changed. Dengue and DHF have evolved as serious emerging infectious diseases causing high morbidity and significant mortality in almost all countries in south-east Asia.

AKI is a poorly studied complication of DHF. The available information comes from small series of patients or case reports. Futrakul *et al.*[7] reported 'mild elevation in serum creatinine' in 43% of 24 DHF cases in Thailand. Tanphaichitr *et al.*[11] found one case of 'transient azotemia' and one case of 'acute renal shutdown' among 17 patients with DHF and G-6-PD deficiency. Méndez and Gonzáles[13] found 1.6% of acute renal failure (ARF) among 617 children with DHF in Colombia. More recently, Lee *et al.*[16] reported 4.9% of ARF in 81 Chinese patients suffering from DHF/DSS and Abboud[17] reported 5% of ARF in DHF. Wiwanitky[18] revised the literature concerning fatal cases of DHF in Thailand, finding 51 fatalities in a total of 6154 DHF cases. Among these patients, 17 had AKI, yielding a percentage of 33.3% of AKI in the patients who died and a percentage of 0.3% of AKI for all DHF cases.[18] Besides these series of patients, there are eight cases of AKI reported in patients with DF[8–10,19,20] and 5 cases reported in DHF or DSS[12,14,15,21, 22]. The mortality rate was very high among these patients (five deaths in 13 cases, 38%).

Renal injury comprising creatinine increase, proteinuria, glomerulonephritis, acute kidney injury (AKI) and haemolytic uraemic syndrome has been reported in dengue patients[6–22]. The higher rate of urinary abnormality is common in acute dengue although abnormal renal function test itself rare. To date, all DHF-induced AKI described cases have occurred in association with shock, haemolysis or rhabdomyolysis [11,12,14,15].

A study done in Thailand by Lumpaopong A et al[23] on serum electrolytes and urine analysis in children with either dengue fever (DF) or dengue hemorrhagic fever (DHF). The prevalence of hyponatremia in patients with DF was 61% and DHF was 72% ($p = 0.149$). The mean serum sodium levels in patients with DF and DHF were 133.5 ± 3.52 and 133.5 ± 3.20 mEq/l ($p = 0.938$), respectively. The prevalence of hyponatremia in patients with mild (grade I), moderate (grade II) and severe (grade III-IV) DHF were 70, 77, and 78% ($p = 0.729$), respectively, and the mean serum sodium levels were 134.1 ± 3.05, 132.9 ± 3.33, and $132.5 + 3.28$ ($p = 0.189$), respectively. The prevalence of hypokalemia in patients with DF was 14% and 17% in patients with DHF ($p = 0.588$). A high urine specific gravity reflecting dehydration was found in 63% of patients with DF and 60% of patients with DHF ($p= 0.77$). The prevalences of hematuria in patients with DF and DHF were 18% and 27% ($p = 0.182$), respectively and proteinuria were 15% and 27% ($p = 0.072$), respectively. The prevalences of hematuria and proteinuria were not different among patients with mild, moderate and severe DHF. No patients had gross hematuria or developed acute renal failure requiring dialysis. Mild hyponatremia is a common electrolyte disturbance and renal involvement is mild in patients with DF and DHF.

In a study done by Gulati[24] where atypical renal manifestations of dengue were reviwed. They described that acute renal failure is rare in dengue fever and it mainly presents as shock induced acute tubular necrosis. It has been observed as a complication of dengue fever in French Guiana (Hommel et al. 1999)[25] and was found to occur in 0.3% of cases in a series of 6154 patients with DHF (Wiwanitkit 2005)[17]. Descriptions of glomerular changes observed in DHF are scarce. They include a variety of signs including IgG, IgM and ∕ or C3 deposition and thickening of the glomerular basement membrane (Boonpucknavig et al. 1976)[7]. Acute renal failure and multiple organ failure can also be a manifestation of rhabdomyolysis (Gunasekera et al. 2000)[10.] Wiwanitkit discovered that the diameter of dengue virus immunoglobulin complex is much smaller than the diameter of glomerulus. Thus he postulated that immune complex can be entrapped only if a previous glomerular lesion causes narrowing of the glomerulus's diameter, and concluded that the immune complex does not play a significant role in pathogenesis of renal failure in dengue infection (Wiwanitkit 2005b)[17]. Renal failure because of haemolytic uraemic syndrome has been described in an isolated case report where renal biopsy revealed thrombotic microangiopathy with glomerular and arteriolar microthrombi. Electron microscopy demonstrated presence of microtubuloreticular structures suggesting a viral infection. This patient was treated with plasmapheresis, haemodialysis and anti-hypertensive drugs (Wiersinga et al. 2006)[19].

Methods and Materials:

Dengue virus infection may involve kidney in dengue patients. This is a cross sectional study that was done in medicine, nephrology and biochemistry department of CMCH and selected private hospital in Chittagong city from 01/07/2019 to 31/12/2019 in hospitalized patients diagnosed as dengue fever. Purposive sampling from 100 consecutive cases of dengue fever was selected. Inclusion criteria includes patients with continued fever, headache, body ache, retro-orbital pain/vomiting/back pain/abdominal pain/rash, absence of convincing evidence of any other febrile illness and excludes known case of CKD, nephropathy due to any known etiology and patients/attendants unwilling to give informed consent to take part in the study. All relevant information for each individual study subject was recorded after getting informed written consent on a pre- tested data sheet and processed and analyzed by using computer bases software SPSS-15. Different statistical methods were applied for data analysis where P value was considered as statistically significant when it is less than 0.05.

Result:

Figure 1: Distribution of patients according to urine examination findings:
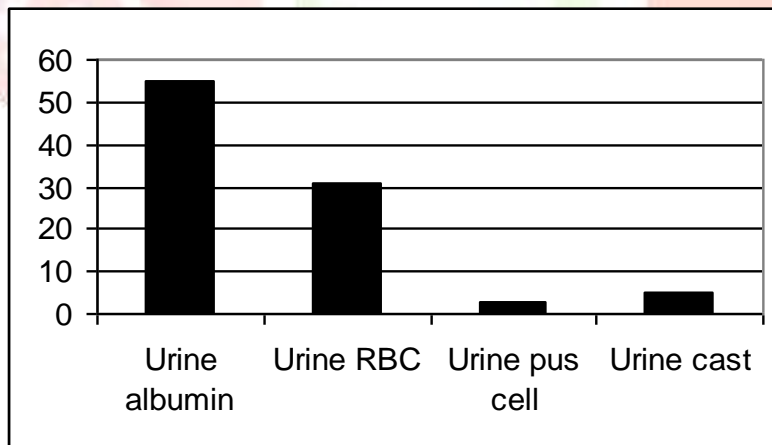
Table 1: Distribution of different lab parameters (n=100)

Parameters	N	Minimum	Maximum	Mean	Std. Deviation
ESR		6	43	18.66	9.076
Total count		2500	12000	6095.00	2787.504
Platelet count	100	20000	320000	13900.00	77207.513
PCV		34	60.50	40.0600	10.19518
Blood urea		12	57	35.33	10.663
Serum creatinine		.80	2.10	1.3995	.30785

Table 2: Outcome of the patients

Outcome	Frequency	Percent	Valid Percent	Cumulative Percent
Improved	82	82.0	82.0	82.0
Referred	11	11.0	11.0	93.0
Died	2	2.0	2.0	95.0
Refused the treatment	5	5.0	5.0	100.0
Total	100	100.0	100.0	

Table 3: Outcome and levels of blood urea and serum creatinine

	Outcome	Blood urea(mg/dl)	Serum creatinine (mg/dl)
Improved	Mean	22.99	1.3573
	N	82	82
	Std. Deviation	8.085	.28373
Referred	Mean	38.45	1.3500
	N	11	11
	Std. Deviation	13.140	.40452
Died	Mean	50.00	1.6182
	N	2	2
	Std. Deviation	14.243	.21213
Refused the treatment	Mean	37.00	1.6300
	N	5	5
	Std. Deviation	16.837	.24393
Total	Mean	25.33	1.3995
	N	100	100
	Std. Deviation	10.663	.30785

Table 4(a): ANOVA test results of blood urea with outcome

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	16.233	18	.902	1.884	.029
Within Groups	38.767	81	.479		
Total	55.000	99			

Table 4(b): ANOVA test results of serum creatinine with outcome

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	18.805	12	1.567	3.767	.000
Within Groups	36.195	87	.416		
Total	55.000	99			

Table 5: Pattern of renal involvement

Parameter	Renal involvement	Number (%)
Blood urea	Above 40 mg/dl	35 (35%)
	Below 40 mg/dl	65 (65%)
Serum creatinine	Above 1.2mg/d	27 (27%)
	Below 1.2mg	73 (73%)
Serum albumin	Above 3gm/dl	93 (93%)
	Below 3gm/dl	7 (7%)

Discussion:

This is a first hospital based study to see the renal involvement among patients of dengue admitted in Chittagong Medical College hospital and selected private hospital in Chittagong.
Among the 100 patients of dengue urine albumin was found among 55% of patients, urine RBC was found in 31% of patients, urine pus cell was found in 3% patients and urine cast was found in 6% of patients. Findings were consistent with the previous findings.[27]

Among the 100 patients mean $\pm$ SD of ESR was 18.66 $\pm$ 9.076 mm in 1st hour, total count was 6095 $\pm$ 2787.504, platelet count was 13900 $\pm$ 77207/cml, PCV was 40.06 $\pm$ 10.19, blood urea was 35 $\pm$ 10.663 mg/dl and serum creatinine 1.39$\pm$ 0.307 mg/dl. This findings also were similar to findings done in earlier study.[26, 27]
Among the 82 improved patients mean $\pm$ SD of blood urea was 22.99 $\pm$ 8.085 mg/dl and creatinine was 1.359 $\pm$ .283 mg/dl. Patients who were referred and died also had mean $\pm$ SD of serum creatinine were 1.35 $\pm$ 0.212mg/dl and 1.6 $\pm$ 0.404 mg/dl and mean $\pm$ SD urea were 38.45 $\pm$ 13.14 mg/dl and 50 $\pm$ 14.24 mg/dl respectively. Results are consistent with the previous study.[18, 21, 22]. Regarding analysis of renal involvement, >40mg/dl urea was found among 35(35%) patients whereas serum creatinine was found >1.2mg/dl among 27(27%) of patients and <3gm/dl serum albumin was found among 7(7%). Findings are consisted with the previous study.[7] Azotemia was associated with high level of mortality which was statistically significant (p<0.05).
In the present study different pattern of renal involvement was described among the patients of dengue. The renal involvement might be due to volume depletion due to plasma leakage. Second important cause might be due to immunological process where immune complexes are deposited in the glomerular basement membrane. Another cause of renal involvement is because of haemolytic uraemic syndrome where thrombotic microangiopathy with glomerular and arteriolar microthrombi play a significant role.

Conclusion:

Renal injury comprising creatinine increase, proteinuria, glomerulonephritis, acute kidney injury (AKI) and haemolytic uraemic syndrome has been reported in dengue patients. To date, all DHF-induced AKI described cases have occurred in association with shock, haemolysis or rhabdomyolysis.

Limitation: This is small sample size study without long term follow up of the dengue patients.

Conflict of interest: There is no conflict of interest of the study.

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