



## Dengue Fever Patients May Develop Proteinuria and Hematuria – A Report of 18 Patients

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### ABSTRACT

*Present study relates to the results of urine analysis of 18 patients with Dengue fever. Dengue antigen (Ag) detection was done in sera of patients with febrile illness by ELISA using monoclonal murine anti-NS1 antibody. All the patients (n = 18) were serum Dengue antigen NS1 positive. Dengue IgM and IgG antibody tests were also done in 11 of 18 NS1 Ag<sup>+</sup> sera using micro ELISA kits; one of 11 patients also had Dengue IgM antibody in his serum. Age of the patients ranged from 11 to 78 (median 43) years. Male female ratio was 2:1. Eight of 18 patients had significant proteinuria (urinary proteins 10 mg/dl or >10 mg/dl). Three other patients had urinary proteins < 10 mg/dl and it was considered insignificant. One of 8 patients had severe proteinuria (200 mg/dl). Five of 18 patients had hematuria; 2 of these 5 patients had 2+ hematuria (6 to 10 rbc/hpf). Four patients had both proteinuria and hematuria. Severe proteinuria might have developed subsequent to thickening of glomerular basement membrane or loss of foot processes. Hematuria might have developed due to injury of glomerular capillaries.*

**Key Words:** *Virus-induced nephropathy dialysis.*

### INTRODUCTION

Recently large number of patients with febrile illness were recorded in our laboratory. First Dengue NS1 positive patient was reported from our laboratory on 30<sup>th</sup> June 2016 and last patient was reported on 26<sup>th</sup> November 2016. Earlier, Dengue fever patients were recorded from an adjoining city of Kanpur during the years 1968

and 1969 and Dengue type 4 and type 2 viruses were isolated<sup>1,2</sup>. Current illness was similar to previous Kanpur patients except for few differences. First, a few patients in current illness developed both proteinuria and hematuria. However, these features were not reported in Kanpur patients. Second, at present Dengue virus DENV-1 and DENV-2 appear to be prevalent in

India<sup>3</sup> while in Kanpur epidemic DENV-2 and DENV-4 were isolated. All the four types of dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4) cause a similar clinical syndrome. In rare cases, second infection with a serotype of dengue virus dissimilar to previous infection may lead to severe disease, suggesting enhancement<sup>4,5</sup>. Moreover, significant biological differences have been shown between strains of the same serotype<sup>6</sup>. Clinically, dengue fever (DF) is characterized by sudden onset of high fever and myalgia for few days, followed by recurrence of fever ('Saddleback' biphasic course). DF may be associated with leucopenia with relative lymphocytosis and thrombocytopenia (platelets <1 lac/mm<sup>3</sup>). In addition, liver enzymes may be raised<sup>6</sup>.

### CASE REPORT

Present study relates to the results of urinalysis of 18 dengue fever patients. Urine analysis was done using Siemens Multistix 10 SG strips. Positive results were later confirmed using conventional manual methods. Microscopic examination of urine was also done. Urinary proteins were estimated by turbidometric method after mixing with Benzethonium chloride using Cobas 6000 (Rosche).

Table 1 shows the results of Dengue antigen and antibody detection tests. Dengue NS1 antigen was detected by one step ELISA using monoclonal murine Dengue NS1 antibody (Patelia<sup>TM</sup> Dengue NS1 antigen kit was purchased from Bio-Rad, France). All the patients were Dengue NS1 antigen positive. Dengue IgM and IgG antibody detection was done by Micro ELISA (Kits were purchased from J Mitra and Company Pvt. Ltd., New Delhi). Dengue IgM antibody was detected in a patient (no.4). On site Typhoid IgG/IgM chromatographic immunoassay was also done with sera of all the patients; all the tests were negative.

Table 2 shows the salient clinical and laboratory findings. Age of the patients (n = 18) ranged from

11 to 78 (median 43) years. Male female ratio was 2:1. Four of 18 patients had ketonuria. Eight of 18 patients (44.4 %) had significant proteinuria (urinary proteins 10 mg/dlor above were considered significant). Most important feature was the detection of severe proteinuria 200 mg/dl in a patient (no.8). Five of 18 patients had microscopic hematuria. Two patients had 2+ hematuria (6 to 10 rbc/hpf). Four patients had both proteinuria and hematuria. Serum creatinine was estimated only in 6 patients; its levels ranged from 0.6 mg/dl to 1.5 mg/dl (normal < 1.5 mg/dl). One of the patients had mild rise in serum creatinine (1.5 mg/dl) along with 2+ hematuria. Serum glutamic pyruvic transaminase (SGPT) was done in 7 patients and all the patients had elevated levels (>40 units/L).

Table 3 shows the haematological findings in patients. Seven of 18 patients had leucopenia. Twelve of 18 patients had thrombocytopenia. One of the patients had severe thrombocytopenia. Five of 14 patients had mild anaemia and 2 other patients had moderate anaemia.

**Table 1** shows results of Dengue virus antigen (NS1) and antibody detection tests

Patient no.	I.D.	Dengue IgM	Dengue IgG	Dengue antigen
1	220495	-	-	+
2	113128	ND	ND	+
3	110351	-	-	+
4	110952	+	+	+
5	112123	-	-	+
6	112514	-	-	+
7	112774	ND	ND	+
8	112776	ND	ND	+
9	113011	-	-	+
10	113481	-	-	+
11	210223	-	-	+
12	130805	-	-	+
13	131513	-	-	+
14	150059	-	-	+
15	151169	ND	ND	+
16	151220	ND	ND	+
17	140880	ND	ND	+
18	104997	ND	ND	+

Abbreviations : - negative, + positive, ND not done.

**Table 2** shows results of urinalysis and biochemical tests in patients.

Patient no.	Lab. No.	Age (years) and Sex	Urinalysis findings					Serum Creatinine mg/dl	SGPT U/L	Result
			Protein mg/dl	Acetone	Pus cells	RBC	Cast			
1	220495	78 M	-	-	-	-	-	ND	ND	
2	113128	18 M	-	3+	-	2+	-	ND	ND	Ketonuria, Hematuria
3	110351	32 F	10	-	±	+	-	0.8	66	Proteinuria, Hematuria, SGPT ↑
4	110952	30 M	80	-	+	+	-	1.1	383	Proteinuria, Hematuria, SGPT ↑↑
5	112123	32 M	5	-	-	-	+	ND	56	SGPT↑
6	112514	43 M	5	-	3+	-	-	1.0	ND	UTI
7	112774	46 M	5	-	+	-	-	ND	ND	
8	112776	55 F	200	-	-	-	-	ND	ND	Proteinuria (3+)
9	113011	50 F	40	3+	+	-	-	0.6	ND	Proteinuria, Ketonuria
10	113481	19 F	-	-	+	-	-	0.6	93	SGPT↑
11	210223	40 M	20	3+	-	-	-	ND	68	Proteinuria, Ketonuria, SGPT↑
12	130805	50 M	10	-	+	2+	-	1.5	ND	Proteinuria, Hematuria
13	131513	47 F	-	-	±	-	-	ND	68	SGPT↑
14	150059	39 M	-	2+	-	-	-	ND	ND	Ketonuria
15	151169	66 M	10	-	+	+	-	ND	92	Proteinuria, Hematuria, SGPT↑
16	151220	35 F	-	-	-	-	-	ND	ND	
17	140880	63 M	10	-	-	-	-	ND	ND	
18	104997	11 M	-	-	+	-	-	ND	ND	

Abbreviations : - negative, + positive (1 to 5 cells/hpf), 2+ (6 to 10 cells/hpf), M male, F female, UTI urinary tract infection.

**Table 3** shows hematological findings in patients.

Patient no.	Lab. No.	TLC mm <sup>3</sup>	Platelets lac/mm <sup>3</sup>	Hb g/dl	Interpretation
1	220495	3000	1.17	12.8	Leucopenia, Thrombocytopenia (+), Anaemia (2+)
2	113128	ND	0.62	ND	Thrombocytopenia (2+)
3	110351	4200	1.00	10.1	Thrombocytopenia (+)
4	110952	4700	0.87	13.9	Thrombocytopenia (2+)
5	112123	7900	1.17	14.3	Thrombocytopenia (1+)
6	112514	2800	0.76	14.1	Leucopenia, Thrombocytopenia (2+)
7	112774	ND	ND	ND	
8	112776	ND	1.5	ND	
9	113011	2900	1.25	9.9	Leucopenia, Thrombocytopenia (1+)
10	113481	2400	ND	12.8	Leucopenia
11	210223	2900	0.58	13.3	Leucopenia, Thrombocytopenia (2+), Anaemia (1+)
12	130805	6600	1.64	12.6	Anaemia (1+)
13	131513	3500	1.20	12.2	Leucopenia, Thrombocytopenia (1+)
14	150059	5200	1.35	13.7	Thrombocytopenia (1+), Anaemia (1+)
15	151169	3000	0.52	12.5	Leucopenia, Anaemia (1+), thrombocytopenia (2+)
16	151220	4700	0.60	10.9	Thrombocytopenia (2+), Anaemia (2+)
17	140880	5000	0.74	12.3	Thrombocytopenia (2+), anaemia (1+)
18	104997	ND	ND	ND	

ND = not done

## DISCUSSION

Most important feature of this study was the detection of proteinuria in 8 of 18 (44.4%) cases of dengue fever (DF). Proteinuria has been detected in as high as 74% of patients with severe dengue infection<sup>7</sup>. The patients with dengue hemorrhagic fever (DHF) had higher median proteinuria levels when compared with DF patients (0.56 Vs 0.08/day p <0.001)<sup>8</sup>. In the present study, a patient (no.8) developed severe proteinuria. Similar massive proteinuria has been described earlier in few patients<sup>7,9,10</sup>. In the later study, proteinuria peaked on eighth day and reduced to trace levels by the tenth day of illness coinciding with normalization of platelet count, suggesting possible role of immune mechanisms in pathogenesis of proteinuria<sup>10</sup>. In another study, proteinuria was found in 15% children with DF compared to 27% those with DHF<sup>11</sup>.

Another important feature of present illness was the detection of microscopic hematuria in 5 of 18 patients (27.78%). Hematuria has been reported earlier in 12.5% patients with DHF<sup>12</sup>. Results of renal biopsy of 20 DHF patients revealed focal thickening of glomerular basement membrane and deposition of immune complexes consisting of IgM, IgG and complement C<sub>3</sub> component<sup>13</sup>. A patient with dengue fever developed acute renal failure due to IgA nephropathy<sup>14</sup>. Another patient with acute glomerulonephritis has been reported earlier<sup>15</sup>. A 22 yrs old female developed lupus nephritis following dengue virus infection<sup>16</sup> (immune deviation). Clearly, findings of different studies suggest that few cases with dengue fever may also develop nephropathy. The prevalence of dengue virus-induced acute kidney injury (AKI) ranges from 0.2% to 10.0% in children and 2.2% to 35.7% in adults<sup>17</sup>. Presence of AKI appeared to increase the mortality of both children and adults from 12% to 44% to >60%, suggesting requirement of renal replacement therapy in selected patients<sup>17</sup>. In addition, patients with renal failure (RF) group had higher mortality rate than non-RF group (28.6% Vs 1.2%, p<0.001)<sup>18</sup>.

In the current study, 12 of 18 patients developed thrombocytopenia. Later feature is known to be associated with proteinuria. In addition, proteinuria appeared to resolve following resolution of the illness<sup>8</sup>. In the present study, two patients had moderate anaemia and 5 other patients had mild anaemia. Anaemia might have developed following infection of bone marrow cells.

In the current study, ketonuria was detected in 4 of 18 patients. Ketonuria might have developed following increased metabolic rate due to high fever. Another interesting feature was the detection of elevated levels of SGPT in all the 7 patients where the liver enzyme was estimated. SGPT may be a biochemical marker of DF<sup>19</sup>. Reye syndrome has been reported in several dengue fever patients<sup>20</sup>. Congenital athymic nude(nu/nu) mice infected with DENV strains might develop fatal encephalitis with viral antigen localization in neurons<sup>20</sup>, suggesting possible role of T-cells in pathogenesis of dengue virus infection.

## CONCLUSION

Few Dengue fever patients may also develop proteinuria as well as hematuria, suggesting nephropathy and renal failure. Reversal of renal dysfunction may occur following dialysis in some cases. In addition, intensive fluid and electrolyte therapy may be required.

**Financial support and sponsorship:** Nil

**Conflicts of interest:** None

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