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Renal Manifestations of Scrub Typhus - in a Tertiary Care Centre of North India 2018-19

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ABSTRACT

Background- Kidney involvement is an important finding in scrub typhus. A retrospective cross sectional study was done to find out the occurrence, course of disease, urinary abnormalities, complications, outcomes and the risk factors determining acute kidney injury (AKI) in cases with scrub typhus.
Methods- Out of 484 admitted patients with acute febrile illness from July 2018 to April 2019, data of 204 patients of Scrub Typhus detected by "IgM ELISA test (titre equal or more than 0.5) were analysed.
Results- Maximum patients 172 (84%) were admitted from August to December and all belonged to rural and semi-urban area. In AKI group there was male preponderance. (OR=6, p<0.05). In 32% of patients urinary abnormality was found. Mean serum creatinine was 2.82±1.67mg/dl.AKI was seen in 72 (35.3%) of patients with stage 1 (33.3%), stage 2 (44.4%) and stage 3 AKI (22.3%). Haemodialysis was required in 12 (16.7%) patients. Overall mortality was seen in 44 (21.56%) patients, and it was higher in cases with AKI (44.4% vs. 9.4%; p <0.005).
Conclusion- Scrub typhus is an important cause of acute febrile illness which causes multiple organ dysfunction syndrome and it is easily treatable but most ignored disease. AKI development in patients of scrub typhus may predict grave prognosis.

Key Words- Scrub typhus, Acute Kidney Injury, Acute respiratory distress syndrome, Shock, hemodialysis

INTRODUCTION

Vector-borne disease Scrub typhus is caused by *Orientia tsutsugamushi* which is transmitted via infected larval forms (chiggers) of trombiculid mites after it's bite.[1] This is a common pathogenic organism in Asia-Pacific, and its incidence is 23% of all acute febrile illnesses.[2] Acute febrile illness is the commonest clinical presentation with nausea, vomiting, rash, myalgia, headache and thrombocytopenia. Main clinical presentation is atypical, causing difficulty in diagnosis in early course, when antibiotics may be effective.[3] Delay in diagnosis and treatment leads to further complications which include multi organ dysfunctions including kidney, liver, lungs, central nervous system, and shock. Renal deterioration may range from 10% to 60% as a result of a number of pathogenic mechanisms. Monocytes, endothelial cells and some other cells become the main infective site for O. tsutsugamushi leading to vasculitis and endothelial dysfunction.[1] Proteinuria, haematuria, pyuria, casts and oliguria are the urinary abnormalities and initials of acute kidney injury.

Highly prevalent disease Scrub typhus is easily treatable but most ignored entity[4], delayed treatment, may increase

mortality up to 30%.[1] In India, in the year 1930, first time it was identified and then in Second World War.[5] In 1938 first case was reported from Kumaon hills of Uttarakhand while serologically confirmed case was first diagnosed in 1945 from Uttar Pradesh.[6] Since then frequency of Scrub typhus is increasing day by day from different ecologies such as southern India, Himalayan regions, desert regions, coastal areas, the plains of northern India and metropolitan cities.[1,7] In 1992 and 2009 a number of patients were diagnosed with Scrub typhus in Uttarakhand while from Uttar Pradesh Scrub Typhus is very uncommon.

METHODS

Study place and design

A hospital based retrospective, analytical and descriptive study was conducted at a tertiary care centre of Uttar Pradesh of north India. The study protocol was approved by the local ethical committee of hospital. Informed consent was taken from each patient.

Study population

Data of admitted patients with acute febrile illness was collected from July 2018 to April 2019 with positive test of Scrub Typhus Detected "IgM ELISA (titer equal or more than 0.5). Out of 484 patients of acute febrile illness admitted, 204 patients (positive for Scrub Typhus) were enrolled in the study.

Patients with at least one of the following feature were suspected for Scrub Typhus

1. Acute-febrile illness with or without headache, pain abdomen, cough with or without shortness of breath, rash, conjunctival infection or lymphadenopathy.
2. Presence of eschar, a primary punched out ulcer.
3. Acute febrile illness like typhoid fever, brucella, dengue, malaria, leptospirosis were ruled out.

History of possible exposure to mite larvae was asked along with investigations and treatment prior to admission. General and systemic examinations were done with main focus on the presence of rash, eschar and lymphadenopathy.

Serological evidence of scrub typhus was obtained by demonstration of IgM antibodies to 56 kDa antigen of O. tsutsugamushi, using a commercial IgM ELISA (Scrub Detect™, InBios International Inc., Seattle, Washington, USA). The cut-off used for the IgM ELISA was an optical density of >0.5 as used in other studies.[8] Data of all enrolled patients were collected.

Data was collected in terms of clinical, biochemical, radiological and demographic variables. Urine routine and microscopic examination for proteinuria, pyuria, haematuria and casts were done in all. AKI was defined according to kidney disease improving global outcome (KDIGO) guideline. All 204 patients were grouped into AKI (72 patients) and non-AKI (132 patients) groups. All variables including clinical, biochemical features, renal manifestations, complications, and outcome were compared between these two groups.

Statistical analysis was performed using SPSS Statistics software. Base line characteristics were assessed with standard descriptive statistics. Quantitative variables were compared using independent t-test and Mann-Whitney test between two groups. Qualitative variables were compared using Chi-square test. $p<0.05$ was considered statistically significant.

RESULTS

Most of the patients were from rural 128 (62.7%) and semi-urban 76 (37.3%) areas.

Maximum patients 172 (84%) admitted in the month between September and December with first case in August. Maximum numbers of patients were admitted in November.

72 (35.3%) developed AKI. The baseline features in AKI and non-AKI are given in (Table 1).

Table 1. Baseline characteristics of AKI and non- AKI groups

No.	Parameters	Without AKI N=132		With AKI N=72		t-value	p-value
		Mean	SD	Mean	SD		
1.	Age (years)	28.6	11.3	32.2	19.78	-0.83	0.408
	Male	45.5%		83.3%			<0.05
2.	Duration of fever (days)	10.5	4.6	12.4	6.55	-1.23	0.223
3.	Pulse (/minute)	85.7	5.22	91.2	6.36	-3.26	0.002
4.	Systolic BP (mmHg)	122.4	22.56	106.9	9.27	-3.18	0.003
5.	Ventilator duration (in days)	4.00	0.00	13.00	1.15	-10.39	<0.001

Age wise distribution of cases

Mean age of the patients with AKI 32.2+_19.8 years and in patients without AKI it was 28.6+-11.3 years. Minimum age was 13 years while maximum was 68 years in all admitted patients. Among patients with AKI, 11% of patients were ≤14 years, 66.7% were between 15 and 59 years, and 22% were more than 60 years of age. The age of the patients was not associated with renal outcome.

Gender wise distribution of cases

Out of 204 positive patients for scrub typhus, 120 (58.8%) were male while 84 (41.2%) were female. In AKI group there was preponderance of male. (OR=6, p<0.05)

Clinical parameters

Fever was present in all the patients along with other clinical presentations in the descending order of frequency were jaundice 116 (57%), nausea and vomiting 112 (55%), anemia 108 (53%), dyspnea 96 (47%), headache 88 (43%), pain abdomen 88 (43%), cough 88 (43%), myalgia 76 (37.25%), anorexia 52 (25.5%), neurologic manifestations 48 (23.5%), cardiac manifestations 44 (21.5%), hemoptysis 36 (17.6%), hearing loss 32 (15.7%), lymphadenopathy 32 (15.7%), eschar 32 (15.7%), sub conjuctival haemorrhage 16 (7.8%), and diarrhoea 4(2%) patient (Table 2). There was no significant difference of clinical presentation between AKI and non-AKI groups except subconjuctival haemorrhage and myalgia that were significantly higher in AKI groups.

Table 2.Comparision of different variables in AKI and non-AKI groups.

No.	Variables		Without AKI		With AKI		chi sq	p-value
			No.	%	No.	%		
1.	Nausea and Vomitting	No	52	39.4%	40	55.6%	1.23	0.268
		Yes	80	60.6%	32	44.4%		
2.	Pain abdomen	No	64	48.5%	52	72.2%	2.68	0.102
		Yes	68	51.5%	20	27.8%		
3.	Anorexia	No	96	72.7%	56	77.8%	0.16	0.692
		Yes	36	27.3%	16	22.2%		
4.	Diarrhea	No	128	97.0%	72	100.0%	0.56	0.456
		Yes	4	3.0%	0	0.0%		
5.	Dyspnea	No	72	54.5%	36	50.0%	0.10	0.756
		Yes	60	45.5%	36	50.0%		
6.	Cough	No	72	54.5%	44	61.1%	0.21	0.651
		Yes	60	45.5%	28	38.9%		
7.	Hemoptysis	No	108	81.8%	60	83.3%	0.02	0.892
		Yes	24	18.2%	12	16.7%		
8.	Subconjuctivalhemorrhage	No	132	100.0%	56	77.8%	7.96	0.005
		Yes	0	0.0%	16	22.2%		
9.	Jaundice	No	68	51.5%	20	27.8%	2.68	0.102
		Yes	64	48.5%	52	72.2%		
10.	Hearing loss	No	120	90.9%	52	72.2%	3.08	0.079
		Yes	12	9.1%	20	27.8%		
11.	Myalgia	No	96	72.7%	32	44.4%	3.99	0.046
		Yes	36	27.3%	40	55.6%		
12.	Headache	No	84	63.6%	32	44.4%	1.75	0.186
		Yes	48	36.4%	40	55.6%		

Laboratory parameters

Anemia was seen in 108 (53%), leukocytosis (total leukocyte counts >11,000/mm ^{3}) in 96 (47%) patients without significant differences in AKI and non-AKI groups and thrombocytopenia (platelet

count <150,000/mm ^{3}) in 140 of patients with 83.33% and 60.6% in AKI and non-AKI groups, respectively. Urinary abnormalities were seen in 32% of patients with hematuria, pyuria, proteinuria and oliguria. Serum K, blood urea and creatinine were significantly higher in AKI group. (p=0.041, p=<0.001, p=<0.001 respectively) while serum Na was significantly lower (p=0.028). Sodium imbalance was seen in 96 patients of which hyponatremia seen in 76 (79%) and hypernatremia in 20 (21%) patients. Potassium imbalance was seen in 52 patients, of which hyperkalaemia 28 (54%) and hypokalaemia 24(46%) was present. Mean serum creatinine was 2.82mg/dl with significant higher value in the AKI group (mean value 2.58 vs. 0.86 mg/dl; p=<0.001). (Table 3)

Table 3.Base line investigations in AKI and non-AKI groups.

No.	Parameter	Without AKI		With AKI		t-value	p-value
		Mean	SD	Mean	SD		
1.	Hb (gm/dl)	9.77	1.98	9.52	1.80	0.44	0.664
2.	TLC (cells/cumm)	12030.91	6198.43	10164.44	2891.95	1.20	0.234
3.	PLT (cells/cumm)	28091.85	34842.95	21445.21	16520.67	0.76	0.450
4.	Na (mmol/l)	142.7	12.64	137.2	4.63	-2.26	0.028
5.	K (mmol/l)	4	0.81	4.41	0.57	2.10	0.041
6.	Urea (mg/dl)	41.85	21.96	122.72	66.49	-6.42	<0.001
7.	Creatinine (mg/dl)	0.86	0.19	2.82	1.67	-6.69	<0.001
8.	Bilirubin (mg/dl)	2.64	2.41	3.93	4.13	-1.42	0.163
9.	SGOT (IU/L)	321.61	555.24	280.61	371.34	0.28	0.780
10.	SGPT (IU/L)	254.95	436.27	142.28	102.75	1.07	0.288
11.	SALP (IU/L)	648.94	446.89	614.61	482.33	0.25	0.800
12.	PT (seconds)	15.96	4.71	16.95	6.22	-0.64	0.527
13.	INR	1.31	0.31	1.37	0.75	-0.44	0.661

Foot Notes: Hb-haemoglobin, TLC-total lecocyte count, Na-sodium, K-potassium, SGOT-serum glutamic-oxaloacetic transaminase, SGPT-Serum glutamic pyruvic transaminase, SALP-serum alkaline phosphatase, PT-Prothrombin time, INR-international normalised ratio

Complications

Commonest complication was pneumonia 172(84%) (bilateral in 40, left sided in 52 and right sided in 40 patients),acute respiratory distress syndrome (ARDS) 40 (39%), followed by acute renal failure 72 (35%), congestive heart failure 44 (21%) and shock in 32 (15.7%) patients (Table 4).

Table 4.Comparision of complications in AKI and non-AKI groups

No.	Variables		Without AKI		With AKI		chi sq	p-value
			No.	%	No.	%		
1.	ARDS	No	108	81.8%	16	22.2%	17.35	<0.001
		Yes	24	18.2%	56	77.8%		
2.	Cardiac manifestations	No	108	81.8%	52	72.2%	0.63	0.426
		Yes	24	18.2%	20	27.8%		
3.	Ventilator need in ICU	No	124	93.9%	56	77.8%	2.93	0.087
		Yes	8	6.1%	16	22.2%		
4.	Proteinuria	No	132	100.0%	0	0.0%	51.00	<0.001
		Yes	0	0.0%	72	100.0%		
5.	Adequate Urine Output	No	0	0.0%	72	100.0%	51.00	<0.001
		Yes	132	100.0%	0	0.0%		
6.	Hemodialysis	No	132	100.0%	60	83.3%	5.84	0.016
		Yes	0	0.0%	12	16.7%		
7.	Hematuria	No	104	78.8%	52	72.2%	0.28	0.597
		Yes	28	21.2%	20	27.8%		
8.	Outcome	Died	12	9.4%	32	44.4%	8.26	0.004
		Live	116	90.6%	40	55.6%		

Outcomes in AKI Group

AKI was seen in 35.3% of patients with stage 1 (33.3%), stage 2 (44.4%) and stage 3 AKI (22.3%). Haemodialysis was required for 12(16.7%) of patients with AKI, the indications of which were anuria and volume overload, severe metabolic acidosis, and persistent hyperkalaemia. Among 72 patients with AKI, 40 (55.6%) of patients had complete recovery with mean serum

creatinine value of 0.83 mg/dl at the time of discharge while 32 (44.5%) expired.

Mortality analysis

Mortality was observed in 44 (21.6%) patients, which was significantly higher in the AKI (32 expiry/15.7%) than in the non-AKI (12expiries/ 5.9%) group (p = 0.004). Major complications leading to death were development of shock (out of 32 patients 20 expired), presence of AKI at the time of admission (out of 72 patients 32 expired), pneumonia (out of 172 patients 44 expiried), and requirement of ICU care and ventilator support (out of 24 patients on ventilator, all 24 expired). Different parameters like ARDS, shock, ventilator duration, were significantly associated with the development of AKI.

DISCUSSION

Scrub typhus is an emerging public health issue and an important cause of pyrexia of unknown origin. In case of delay in diagnosis, it may be fatal with significant morbidity and mortality. This is an occupational disease of peoples living in rural area involved in cattle rearing.[9] Doxycycline is antibiotic of choice for its treatment. Our study is the first in Uttar Pradesh to comprehensively describe the way of kidney involvement in Scrub Typhus patients along with description on its clinical features, complications and outcome. In this study we observed that 35.3% patients developed AKI.

Orientia tsutsugamushi is an intracellular gram negative coccobacillus which causes scrub typhus, transmitting by bite of an infected trombiculid mite larva.[10] In 1899 first time scrub typhus was recognised in Japan when mortality rate was 7% to 9%.[11] In the current days, scrub typhus is endemic to a part of the world known as the geographical "tsutsugamushi triangle".[12] Favourable season for its occurrence is the rainy season and in months from July to November.[13]

Larval stage of scrub typhus is responsible for transmitting diseases to vertebral animals including human beings. Incubation period ranges from 10-12 days with initial symptoms of acute febrile illness to severe complication of multiple organ failure and death. Eschar is area of bite of mite in the body which is rarely found in Indian subcontinent.[14] In this study eschar was found in 15.7% patients. Painful lymphadenopathy is found in 13%-18% patients and similar finding of 15.7% of patients in this study had lymphadenopathy. Cause of mortality is mainly respiratory distress and encephalitis.[15] No significant association was found in clinical presentation of AKI and non-AKI groups except subconjuctival haemorrhage and myalgia that were significantly higher in AKI groups.

Renal manifestations are due to number of etiologic factors which includes multiple organ dysfunction syndrome, shock or hypovolemia or increased vascular permeability (decreases renal perfusion and hence AKI),acute interstitial nephritis, rhabdomyolysis, thrombotic microangiopathy secondary to disseminated intravascular coagulation, vasculitis, and acute tubular necrosis.[16,17] Acute tubular necrosis, interstitial nephritis, and mild mesangial glomerulonephritis are the histopathological findings.[17] In this study development of pneumonia, ARDS, shock and multiple organ failure were the major responsible cause for renal manifestation.

Meningoencephalitis, AKI, GI bleeding, myocarditis, pneumonia, ARDS, multiorgan failures and shock are the major complications of scrub typhus that may be fatal. In this study pneumonia, ARDS, AKI, shock and multiple organ dysfunction syndrome were the major observed complications.

In scrub typhus urinary abnormalities are found in 50%-80% [18] of patients while in our study, urinary abnormalities were seen in 32% of patients with hematuria (23.52%), proteinuria (35.29%), oliguria (35.29%) and pyuria. Attur *et al*. reported urinary findings of proteinuria in 28.6%, active sediments, granular casts, hematuria, and pyuria in a

study of scrub typhus patients in South India.[17]

We find 35.29% of the AKI among all 204 admitted patients with similar findings in other studies reporting 10%-60% of kidney involvement.[19] AKI with thrombocytopenia, requirement of intensive care and myocarditis [20] were described in South Indian study of scrub typhus.

Mortality was observed in 44 (21.56%) patients, which was significantly higher in the AKI (32expiry/ 15.68%) than in the non-AKI (12 expiries/ 5.88%) group (p = 0.004). In other studies of scrub typhus it was from 0.79% to 12%.[21] In study of Vivekanandan *et al*. mortality was found to be 12.2% 20, by Kumar *et al*. it was 16.32%.

CONCLUSIONS

Scrub typhus is an important cause of acute febrile illness which causes multiple organ dysfunction syndrome and it is easily treatable but most ignored disease. AKI development in patients of scrub typhus may predict grave prognosis.

Limitations of the Study

This was a retrospective cross-sectional study. Further long term observation and clinical data would be required. ELISA test for scrub typhus may give false positive results due to cross reacting antibodies and hence nucleic acid amplification test would be better for confirmation.

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Conflict of Interest-None

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