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Clinical presentation of scrub typhus during a major outbreak in central Nepal

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ABSTRACT

Background: Scrub typhus, an emerging rickettsial disease caused by the organism *Orientiatsutsugamushi*, is associated with multi-organ involvement. We prospectively studied the clinical manifestations of the disease during a major outbreak in central part of Nepal. **Aims and Objective:** This study was carried out with an aim to analyze the clinical presentations, laboratory parameters, complications and outcomes of scrub typhus. **Materials and Methods:** A prospective observational study was conducted in the Department of Medicine in a tertiary teaching hospital. A total of 1398 patients admitted with acute febrile illness were subjected for Scrub Typhus Detect™ IgM ELISA test, among which 502 (35.90%) patients tested positive and were included in the study. Acute kidney injury was defined according to KDIGO guideline. Statistical analysis was done with SAS University Studio package using t-test for continuous variables and chi-square test for categorical variables. **Results:** Mean age of the patients was 30.37 ± 18.81 years with 26.29% in the pediatric age group (< 14 years). Females comprised of 55.98% of the patients. Majority (97.98%) of the patients were seen between July to November. Clinical presentations in the descending order of frequency were anorexia (55.18%), headache (53.39%), lymphadenopathy (15.73%), jaundice (13.35) and eschar (6.57%). Mean scrub typhus IgM ELISA value was 2.17. Leukocytosis was seen in 5.78% and thrombocytopenia in 66.73% of patients. Transaminitis was found in 80.68% of patients. Urinary abnormalities were recorded in 42.3% of patients. Acute kidney injury (AKI) was seen in 35.8% of patients followed by acute respiratory distress syndrome (24.1%), pneumonia (22.1%), shock (14.74%), neurologic manifestation (6.37%) and cardiac manifestations (4.38%). ICU admission was required for 18.73% of patients and 8.57% required ventilator support. Mortality rate was 1.79%. **Conclusion:** Scrub typhus, being an emerging vector borne infectious disease in Nepalese context, is associated with multiple organ involvement.

Key words: Acute febrile illness, Acute kidney injury (AKI), Hematuria, Albuminuria

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INTRODUCTION

Scrub typhus is a rickettsial disease caused by the organism *Orientia tsutsugamushi* and transmitted through the bite of larval forms (chiggers) of trombiculid mites.[1] It presents as either a non-specific febrile illness with constitutional symptoms such as fever, rash, myalgias and headache or with multi-organ dysfunctions involving organs such as kidney, liver, lungs, central nervous system or with circulatory collapse.[2]

Scrub typhus as a cause of acute febrile illness in Nepal was first reported in 1981.[3] Hospital based study conducted in 2004 in central Nepal found scrub typhus as a cause of acute febrile illness in 3% of patients.[4] Since then the disease has been considered to be endemic in different parts of the country, though it did not cause significant problems. After a 7.5 magnitude earthquake in April 2015, major outbreak of scrub typhus was noted in different districts of central Nepal. So, this study was carried out with an aim to analyze the clinical

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presentations, laboratory parameters, complications and outcomes of scrub typhus.

MATERIALS AND METHODS

A prospective analytical study was conducted from April to December 2016 in the Department of Medicine at Chitwan Medical College Teaching Hospital, a tertiary care institution located in Central Nepal. Approval from the ethical committee and informed written consent from the patients were taken prior to the study. Patients admitted with acute febrile illness (AFI) who were tested positive for Scrub Typhus Detect™ IgM ELISA test (titer equal or more than 0.5), were included in the study. Patients who concomitantly had other infections like dengue, laptopirosis, typhoid fever, brucella or malaria were excluded from the study.

Demographic, clinical and laboratory variables were recorded in all patients. All patients had a detailed clinical history and examination, a standard set of investigations including complete blood counts, liver function tests, serum urea, creatinine, electrolytes, chest radiograph and ultrasonography of abdomen and pelvis. Leukocytosis was defined as white blood cells [WBC] >12000 cells/mm3, anemia as hemoglobin <10 gram/dL, thrombocytopenia as platelets <1.5 lakhs/mm3, elevated bilirubin as total bilirubin >3 mg/dL and elevated aspartate aminotransferase and alanine aminotransferase as four times the normal. Urinary abnormalities were defined by dipstick proteinuria, pyuria, hematuria and casts as seen on urine microscopy and Acute Kidney Injury (AKI) was defined as per kidney disease improving global outcome (KDIGO) guideline.[5] Patient characteristics were summarized using mean and frequency distributions. Data for continuous variables were expressed as mean ± standard deviation using t-test for continuous variables and chi-square test for categorical variables. Analysis of Variation (ANOVA) tests were done to test the differences of continuous variables across multiple groups. Descriptive and inferential statistical analysis were done by using SAS University Studio package.

RESULTS

Out of 1398 patients with AFI subjected for Scrub Typhus Detect™ IgM ELISA test, 502 (35.90%) patients were tested positive. Mean age of the patients was 30.37±18.81 years with an age range between 1 to 79 years (Table 1). Almost 26% of the patients were in the pediatric age group (<14 years). Females comprised of 55.98% of the patients with female to male ratio of 1.26:1.

Majority of the patients were from the plain area (72%) of the country and most of them were from the rural (32%) and semi-urban (24%) areas (Figure 1).

The first case of scrub typhus during this outbreak was seen in April and majority (97.98%) of the patients were seen between July to November with highest number of patients seen in October (Figure 2).

All 100% patients included in the study had fever. Other clinical presentations in the descending order of frequency were anorexia, headache, lymphadenopathy, jaundice and eschar. Urinary abnormalities in 42.3% of patients (Table 2).

Most common complication seen was acute kidney injury (AKI), of which 66% had stage 1, 33% had stage 2 and 1% had stage 3 AKI. Hemodialysis was required in 1.79% of patients. Other complications in descending order were

Table 1: Baseline clinical characteristics

Variables	Mean±SD
Age (years)	30.37±18.81
IgM ELISA value	2.17±1.70
Days in the hospital	5.39±2.32
Days in ICU	1.07±2.35
Duration of fever (days)	5.57±1.22

Table 2: Clinical presentations of scrub typhus

Clinical parameters	Number (%)
Anorexia	277 (55.18)
Headache	268 (53.39)
Lymphadenopathy	79 (15.73)
Jaundice	67 (13.35)
Eschar	33 (6.57)

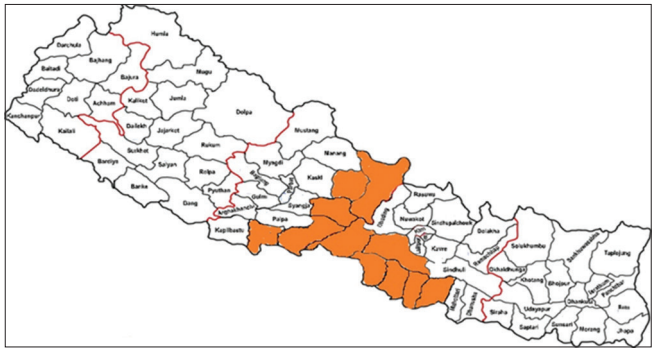

Figure 1: Geographic distribution of the patients

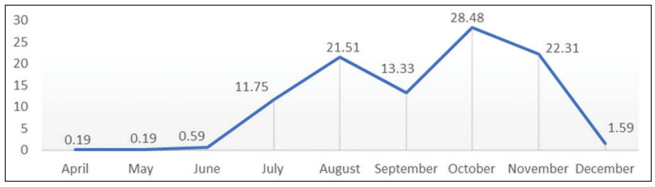

Figure 2: Month-wise distribution of patients

acute respiratory distress syndrome (ARDS), pneumonia, shock, neurologic manifestation and cardiac manifestations. Admission to ICU was required for 18.73% of patients with mean duration of ICU stay of 1.06 days. Mechanical ventilation was needed for 8.57% of patients. Nine patients died with a mortality rate of 1.79% (Table 3).

Leukocytosis (WBC count >11,000/mm3) was seen in 5.78% and thrombocytopenia in 66.73% of patients. Transaminitis was seen in 80.68% of patients with majority having raised AST than ALT (90.63 versus 86.65%; p=0.531). Mean scrub typhus IgM ELISA value was 2.17 (Table 4).

DISCUSSION

This is the first report to comprehensively document the clinical presentation, laboratory investigation, pattern of renal involvement and outcome in a cohort of patients of scrub typhus in Nepal. We have found that scrub typhus was responsible for about 36% of patients presenting with unexplained febrile illness.

Scrub typhus is a vector borne disease caused by Orientia tsutsugamushi, an obligate intracellular gram negative bacteria and transmitted by the bite of an infected Trombiculid mite larva.[6] The disease was first described from Japan in 1899 and in the initial days the overall mortality varied from 7% to 9%.[7] In the current days scrub typhus is endemic to a part of the world known as the "tsutsugamushi triangle", which extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south and to Pakistan in the west.[8] In Nepal, first study to detect scrub typhus was done in 1981 in eastern part of the country where 10% of study population were found to have antibodies to scrub-typhus rickettsiae, indicating that the infection occurred widely in eastern Nepal.[3] In another study, up to 3% of in-hospital patients in central Nepal were found to be infected with the scrub typhus.[4] However, till date there had not been such a large outbreak and clinical study of scrub typhus in the country. Current outbreak of scrub typhus in Nepal was seen from those areas which were affected by the 7.8 magnitude earthquake in April 2015.[9] These outbreaks were thought to be due to people and rodents living in close proximity in temporary shelters after the earthquake.[10,11] Majorities of the patients included in our study were from the earthquake affected areas (Figure 1).

Table 3: Complications in scrub typhus

Complications	Number	Percentage (mean±SD)
AKI	180	35.82±23.72
ARDS	120	24.10±42.81
Pneumonia	110	22.1±41.54
ICU admission	94	18.73±58.24
Shock	74	14.74±35.49
Ventilatory support	43	8.57±28.01
Neurologic manifestation	32	6.37±24.45
Cardiac manifestation	22	4.38±20.49
Death	9	1.79±13.28

Table 4: Baseline laboratory parameters

Parameter	Value (mean±SD)
TLC (cumm)	7327.63±2364.82
Hb (gm%)	10.26±0.98
PLC (cumm)	116689.86±58172.49
AST (U/L)	72.48±53.09
ALT (U/L)	64.40±44.93
Urea (mg/dL)	30.09±12.05
Creat (mg/dL)	1.36±0.69
Scrub ELISA	2.17±1.70

TLC: Total leucocyte count, PLC: Patelet count, AST : Aspartate aminotransferase, ALT: Alanine aminotransferase

The bite of the mite leaves a characteristic black eschar. The adult mites have a four-staged lifecycle viz. egg, larva, nymph and adult. The larval stage, also known as chigger, is the only stage that can transmit the disease to humans and other vertebrates.[6] The incubation period of scrub typhus in human is around 10-12 days and the clinical manifestation varies from mild febrile illness to severely fatal multiorgan dysfunction syndrome. Apart from the non-specific generalized clinical features like fever, malaise, anorexia, headache, lymphadenopathy and cough,[12] the significant findings of scrub typhus is eschar formation at the site of bite, the prevalence of which is variable ranging from 7% to 80%.[13,14] However, eschar is rarely seen in south East Asia and Indian subcontinent.[15,16] Lymphadenopathy usually painful, is a common finding in scrub typhus reported in 13 to 18% of patients.[17-19] In this study, all patients had fever followed by anorexia, headache, jaundice and lymphadenopathy. Eschar formation was seen only in 8% of the patients.

Diagnosis of scrub typhus requires a high degree of clinical suspicion, which is confirmed serologically by different laboratory investigations.[20] The cheapest test currently available and used extensively in Indian subcontinent is Weil- Felix test which is highly specific, but lacks sensitivity.[21,22] Immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) using the 56 kDa antigen has been widely used, which is easy to perform, gives quick results and has sensitivity of 84 to 86% and a specificity of 98%[23,24] and is well validated.[25] No current diagnostic test is sufficiently practical for use by physicians working in rural areas. A new dipstick test using a dot blot immunoassay format appears to be the best currently available test for diagnosing scrub typhus in rural areas where this disease predominates.[26]

Reported severe clinical manifestations or complications of scrub typhus include AKI, meningoencephalitis,

myocarditis, pneumonia, ARDS, AKI, GI bleeding, septic shock, and multiple organ failures which may be potentially fatal if there is a delay in diagnosis and treatment.[27-33] Acute kidney injury (AKI) and renal involvement in scrub typhus is believed to be multifactorial in origin. Overall, renal involvement is considered to be a part of multi-organ dysfunction syndrome in patients with severe disease. In this study, 35.8% of the patients developed AKI, which is consistent with findings in other studies where its incidence has been reported ranging from 10 to 60%.[32-36] Most of the patients had stage 1 and 2 AKI comprising of 66% and 33% respectively and only 1% of patients had stage 3 AKI.

Urinary abnormalities have been reported in 50% to 80% of patients with scrub typhus.[37] Attur et al in their study from south India reported urinary abnormalities in all patients with AKI.[32] Urinary abnormalities were seen in 52.94% of patients with proteinuria being the most common presentation (23.71%) followed by hematuria (17.73%) pyuria (5%) gross hematuria (4.5%) and dipstick positive glycosuria (2%). The incidence of these urinary abnormalities suggest intrinsic renal involvement being the most likely explanation.

Mortality was 1.79%, which was significantly higher in the AKI than in the non-AKI group (2.96% versus 1.0%; p=0.005). Higher rate of mortality in AKI patients could be the reflection of underlying severity of disease. Our finding is comparable to other studies, which ranged from 0.79% to 12%.[38,39] Vivekanandan et al on their study from south India reported the mortality of 12.2%. Lower mortality in our study was probably due to early diagnosis and initiation of treatment. Delayed presentation, acute respiratory distress syndrome and shock have been shown to be the determinants of mortality in previous studies.

There are certain limitations to our study. This was a single center study done in central Nepal and might not reflect the national scenario as the outbreak of scrub typhus had been reported from other areas of the country as well. Secondly, the diagnosis of scrub typhus was made based on the ELISA test and we excluded patients with equivocal results (ELISA titer between 0.2 and 0.5). Although the ELISA method has a satisfactory sensitivity and specificity, nucleic acid amplification tests would bring better results.

CONCLUSION

Scrub typhus is an important cause of febrile illness with multisystem involvement in Nepalese context. If clinicians do not consider a possibility of Rickettsial diseases in a patient with fever, work up for AFI may become difficult and expensive. So, we suggest that scrub typhus should be part of the differential diagnosis in patients with acute febrile illness.

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Authors Contribution:
AS- Concept and design of the study, collection of data, reviewed the literature, manuscript preparation and critical revision of the manuscript; **GRB-** Data analysis, literature review and review of manuscript

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