

Original Research Article

Scrub typhus in North India: clinical spectrum, laboratory parameters and treatment outcome in tertiary care teaching hospital

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ABSTRACT

Background: Scrub typhus is an acute febrile illness causing serious complications leading to significant mortality especially if there is delay in diagnosis and treatment. It is caused by *Orientia tsutsugamushi* a gram negative bacterium and transmitted by the bite of the trombiculid mite (chigger). This study was undertaken to document the clinical manifestations, laboratory parameters and treatment outcomes of scrub typhus cases.

Methods: This retrospective study was done in a tertiary care teaching hospital which included 40 confirmed cases of scrub typhus. The diagnosis was confirmed by positive IgM ELISA. Clinical spectrum and manifestations, laboratory parameters and course in hospital with outcomes were evaluated. Factors associated with complications and mortality were analyzed.

Results: The mean age of the patients was 40 ± 15 yrs with almost equal proportion of males and females (47.5 vs 52.5%). The most common presenting symptoms were Fever (100%), shortness of breath (40%), altered sensorium (22.5%), nausea/vomiting (10%), and diarrhea (7.5%). Mean duration of fever before presentation to hospital was 11.1 ± 4.9 days. Eschar was seen in 15% of patients. Common laboratory abnormalities documented was thrombocytopenia (85%), elevated transaminases (57%) leukocytosis (45%), and leucopenia (15%). About 37.5% of patients developed multiple organ dysfunction syndrome (MODS) with case fatality rate was 10%. Acute renal failure, acute hepatitis, need of ventilator support and CNS dysfunction was higher among patient with MODS.

Conclusions: Scrub typhus patients can have a wide range of manifestation ranging from mild illness to serious and life threatening complications like acute respiratory distress syndrome, acute renal failure, and acute hepatitis and CNS dysfunction. High index of suspicion with early recognition and treatment is key for good outcome. Use of empirical doxycycline may be lifesaving.

Keywords: Acute respiratory distress syndrome (ARDS), Eschar, Multiple organ dysfunction syndrome (MODS), Scrub typhus

INTRODUCTION

Scrub typhus is an acute febrile illness caused by an obligate intracellular gram negative bacterium '*Orientia tsutsugamushi*'. During the Second World War, scrub typhus caused a major epidemics resulting in significant mortality and morbidity in the border regions of India and Burma.¹ In India, studies in the 1960s and 1970s have shown the endemic nature of Scrub typhus in many states

and union territories, the first reported cases were from Himachal Pradesh.² Scrub typhus accounts for up to 23% of all febrile episodes, with an estimated 1 million cases occurring annually, in endemic areas. Scrub typhus is an important cause of acute febrile illness in India.

Although the disease was silent for several decades, there seems to be a resurgence of the disease now. Previously considered as diseases of rural areas but now the disease

has been urbanized and the prevalence has broadened further.

Scrub typhus is transmitted to humans by the bite of the larval stage of the trombiculid mite (chigger) of the *Leptotrombidium* genus, which typically feeds on wild rats. The pathophysiological hallmark of scrub typhus is disseminated vasculitis.³ *O. tsutsugamushi*, from the chigger's digestive system enter into human host and it infect the various cells, including endothelial cells and phagocytes causing an acute vasculopathy, leading to various potential life threatening complications. Prevalence is more during rainy and winter seasons. As in India, increased humidity after the rainy season favors hatching of mite eggs into chiggers which leads to transmission of scrub typhus.⁴

Clinical manifestation can range from a self-limiting disease to a fatal illness in 35-50% of cases, with multiorgan dysfunction, if not promptly diagnosed and treated.⁵ Patient usually present with fever, headache, myalgia, malaise, rash, lymphadenopathy, hepatomegaly, splenomegaly and jaundice.⁶ An Eschar is seen at the site of inoculation which is highly suggestive of scrub typhus but is reported to occur in variable proportion of patients (10-92%).⁷ It usually seen in Axilla, Groin, Inguinal region and is characteristic of scrub typhus. Severe complications including ARDS, Acute Hepatitis, Acute Renal failure, CNS dysfunction, Meningoencephalitis, Myocarditis, and Shock may be seen. Weil-Felix test is a very insensitive and nonspecific test for diagnosis of scrub typhus.¹¹ Gold standard for diagnosis is IgM ELISA testing or Immunofluorescence assay (IFA).

The goal of this retrospective study was to provide clinical and laboratory profile of the scrub typhus patients and to know the outcomes and complications of such patients presenting to our tertiary care teaching hospital.

METHODS

Study type: Retrospective observational study.

Study place: Pt B.D Sharma Post Graduate Institute of Medical Sciences, Rohtak.

Study duration: Aug-2018 to Oct-2019.

Procedure: We reviewed the hospital records of patients with confirmed diagnosis of Scrub typhus admitted in Medicine department. Patients aged more than 15 years with confirmation of scrub typhus based on positive IgM Scrub typhus by ELISA were included expect one patient who was confirmed on the basis of Weil-Felix test in background of strong clinical suspicion was also included. Patients who had incomplete medical records were excluded from study population.

A total of 40 confirmed cases of scrub typhus were included and evaluated retrospectively in this study. A

detailed clinical examination, including presence of an eschar was documented for each patient. Basic laboratory parameters were evaluated including complete hemogram, renal function and liver function test, chest x-rays and complications during treatment and final outcome were documented for each patient. This retrospective study did not require patient informed consent, in accordance with the current rules of our hospital.

Criteria used for various complications

Acute respiratory distress syndrome (ARDS) - Berlin definition: Acute onset of non-cardiogenic pulmonary edema manifesting with bilateral alveolar or interstitial infiltrates on chest radiograph and $\text{PaO}_2/\text{FIO}_2 \leq 300$ mmHg on arterial blood gas analysis. mild ($200 \text{ mmHg} < \text{PaO}_2/\text{Fio}_2 \leq 300 \text{ mmHg}$), moderate ($100 \text{ mmHg} < \text{PaO}_2/\text{Fio}_2 \leq 200 \text{ mmHg}$), and severe ($\text{PaO}_2/\text{Fio}_2 \leq 100 \text{ mmHg}$).⁸

Acute hepatitis: elevation of transaminases ≥ 3 times of upper normal limit and Serum Bilirubin $> 2.5 \text{ mg/dl}$.

Acute renal failure: KDIGO criteria for AKI - AKI is defined as any of the following (Not Graded):

Increase in serum creatinine by $\geq 0.3 \text{ mg/dl}$ within 48 hours; or, increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or, urine volume $< 0.5 \text{ ml/kg/h}$ for 6 hours.

Multiple organ dysfunction syndrome (MODS) - features of two or more organ dysfunction.

Statistical analysis

Statistical analysis was performed using SPSS software. Descriptive data are given as mean \pm SD or as median and interquartile range (IQR). Chi-square test or Fischer's exact test was used to compare dichotomous variable and T-test or Mann-Whitney test was used for continuous variable, as appropriate.

RESULTS

Forty patients admitted with scrub typhus were included in the study. The proportion of males and females were almost equal (47.5 vs 53.5%). The mean age of the patients was 40 ± 15 years. The mean duration of fever before presentation to the hospital was 11.1 ± 4.9 days. The most common presenting symptoms were Fever (100%), shortness of breath (40%), altered sensorium (22.5%), nausea/vomiting (10%), diarrhea (7.5%). An Eschar was seen in 15% of the patients. Common laboratory findings included thrombocytopenia (85%), raised aminotransferase level (57%), leukocytosis (45%), Hyperbilirubinemia (20.6%) and leucopenia (15%). On physical examination hepatomegaly seen in 42.5% and

splenomegaly seen in 7.5% of patients. About 32.5% of patients of patients developed MODS. The case fatality rate for those who developed MODS was higher than that of those who did not (23 vs 4.3%). The overall mortality rate was 10%. The patient's characteristics are provided in Table 1 and Table 2.

Table 1: Patient characteristics.

Parameters	All patients
Age, years (mean±SD)	40±15
Sex M/F (N/N)	19/21
Duration of Fever, days (mean±SD)	11.1±4.9
Symptoms, N (%)	
Fever	40 (100%)
Shortness of breath	16 (40%)
Altered sensorium	9 (22.5%)
Nausea/vomiting	4 (10%)
Diarrhea	3 (7.5%)
Signs, N (%)	
Hepatomegaly	17 (42.5%)
Eschar	6 (15%)
Splenomegaly	3 (7.5%)
Laboratory values	
WBC count, x10 ³ /μl, median(IQR)	9.5 (5.5-12.75)
Platelets count, x10 ³ /μl, median(IQR)	60.0 (37.0-80.0)
Serum Bilirubin, mg/dl, median(IQR)	1.1 (0.75-1.25)
AST, IU/l, median(IQR)	113 (59.5-202)
ALT, IU/l, median(IQR)	82 (44.5-194)
Serum creatinine, mg/dl, median(IQR)	1.35 (0.92-1.97)
Duration of hospital stay, days, mean±SD	5.86±2.0
Treatment	
Azithromycin	3 (7.5%)
Doxycycline	36 (90%)
Azithromycin+Doxycycline	1 (2.5%)

Abbreviations: M, male; F, Female; SD, standard deviation; n, number; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; IQR, Interquartile range.

Complications: Almost one half of the patient developed at least one systemic complication. The most common complication encountered were ARDS (37%), acute renal failure (25%), acute hepatitis (20.6%). AKI and acute hepatitis were seen in most patients who developed MODS (Table 3). No relation was observed between MODS and ARDS however there was increase need of ventilation in MODS patients. About 37% of patients developed ARDS of which 53% of patients required ventilator support. Those patients who presented with Shortness of breath was having higher mortality rate (p<0.01) and those who developed ARDS was having higher mortality rate (p<0.006).

Table 2: Characteristics in patients with MODS and without MODS.

Parameters, mean±SD	MODS absent	MODS present
Age, years, mean±SD	39.6±14.6	42.3±15.9
Duration of Fever, days	10.41±4.39	12.54±5.73
WBC count, x10 ³ /μl	9.3±4.2	10.7±7.3
Platelet count, x10 ³ /μl	76.8±52.5	51.5±21.8
Serum Creatinine, mg/dl	1.33±0.61	2.30±1.42
AST, IU/l	155±364	310±210
ALT, IU/l	81±103	206±93
Serum bilirubin, mg/dl	1.4±2.4	2.4±1.8
Duration of hospital stay, days	5.68±1.79	6.25±2.59

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Co-infection was noted in 6 patients, 4 patients were IgM leptospira positive, were treated with doxycycline and ceftriaxone and 2 patients were dengue NS1 positive. None of the co-infected patient developed MODS or died. Two patients were pregnant women, both were treated with azithromycin, one patient developed MODS followed by recovery without any obstetric complications.

Table 3: Complications in patients with scrub typhus.

Complications	No (%)	MODS present N (%)	MODS absent N (%)
Acute Renal failure	10 (25)	7 (53.8)	3 (11.1)
Acute Hepatitis	6 (15)	4 (40)	2 (10.5)
CNS Dysfunction	9 (22.5)	6 (46)	3 (11.1)
Hepatomegaly	17 (42.5)	7 (53.5)	10 (37)
ARDS	15 (37)	4 (30)	11 (40.7)
Need of Ventilator	8 (20)	4 (30)	4 (14.8)

DISCUSSION

Scrub typhus is a potentially fatal infection that affects about one million people every year.¹³ Multiple organ dysfunction was reported in 32.5% of patients and 37% of patients developed acute respiratory distress syndrome of which 53.3% of patients required ventilator support. Incidence of acute respiratory distress syndrome was on higher side in our study as compared to previous studies from India, which have shown an incidence of 8-10%.^{9,10} The case fatality rate in those with ARDS was 26.6% in our study.

In our study the overall mortality was 10% which was on lower side as compared to previous studies. Reports from northern India have also shown a trend towards decreasing mortality, with a rate of 17.2% reported in 2004 and 14% reported in 2006 and this trend may be due

to increased awareness with early recognition and treatment of the cases.^{9,11} Acute renal failure was seen in 25% of patients, this incidence of renal impairment is almost similar to the incidence (23.2%) reported by Attur et al.¹² and much lower than the 66.4% incidence reported by Mahajan et al.⁹ The rate of finding an Eschar in our study was 15% which is slightly higher than the 9.5% reported by Mahajan et al while an eschar was noted in 46% of patients by Vivekanandan et al in pondichery, and in Korea an eschar has been documented in as many as 90% of patients.^{9,10} This variation in prevalence of an eschar may be due to inappropriate examination and different geographical distribution of the various strains of the organism.

In our study about 85% of patients had thrombocytopenia (less than 1 lakh/ μ l) and about 17.5% of patients had platelet count less than 30000/ μ l. However, the incidence of thrombocytopenia reported from northern China suggest significantly lower rates of thrombocytopenia, ranging from 4.6% to 48.9%¹³ but studies from India have shown similar incidence of thrombocytopenia as reported in our study.^{14,15} In our study leucocyte count had a wide variation with a range from minimum $2.2 \times 10^3/\mu$ l to maximum $27 \times 10^3/\mu$ l. About 15% of patients had leucopenia and 45% of patients had leukocytosis, leucopenia was also reported in 12% of patients by Sivaranjan et al.¹⁶

Drug of choice is Doxycycline 100 mg twice daily for 7 days, therapeutic response to doxycycline therapy is used as a diagnostic test.¹⁷ Alternatively azithromycin can be used and is a preferred drug in pregnancy. Rifampicin (600-900 mg daily for 7 days) may be considered where doxycycline resistance is present.¹⁸ In our study nearly all patient received doxycycline except 3 patients who have received azithromycin and one patient received both azithromycin and doxycycline and responded to both medication well with resolution of symptoms within 3-4 days.

One of the limitation of the study is that the lower number of cases. Strain variation and its virulence, which have shown to be associated with severity of the symptoms and clinical presentation were not explored.^{19,20}

CONCLUSION

Scrub typhus is a more prevalent and serious acute febrile illness associated with significant mortality. ARDS, acute hepatitis, acute renal failure, and CNS dysfunctions are the serious life threatening complications of the disease. Mortality is significantly higher in patient with respiratory dysfunction, ARDS, MODS. Clinician should remain more vigilant for these complication and early diagnosis and treatment can improve the mortality and morbidity in such patients. Use of empirical doxycycline may be lifesaving when clinical suspicion is high.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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