ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Clinical and investigative profile of scrub typhus patients at a tertiary care center in Southern West Bengal, India

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Submission: 20-09-2023 Revision: 26-12-2023 Publication: 01-02-2024

ABSTRACT

Background: Scrub typhus, caused by *Orientia tsutsugamushi*, is an acute febrile illness with symptoms such as fever, chills, and organ failure. The similar clinical presentation in other common diseases such as malaria, dengue fever, and typhoid fever creates difficulty and delay in the clinical diagnosis of scrub typhus. This delay may increase the risk of scrub typhus complications. In India, it is a public health issue with a paucity of data. **Aims and Objectives:** This study aims to evaluate the clinical characteristics, outcomes, and prognostic factors of patients with scrub typhus. **Materials and Methods:** This institutional-based observational, cross-sectional study was conducted among consecutively selected 154 adult patients suffering from scrub typhus at a Medical College Hospital situated in the southern part of West Bengal, India. All data were collected according to a pre-designed proforma. At the end of the study, results were analyzed statistically. **Results:** Younger, females, and homemakers are more susceptible to scrub typhus, mostly in the post-monsoon season from July to November. The incidence of scrub typhus complications is high in the southern part of West Bengal. The case fatality rate of scrub typhus is 6.5%. Male sex, pre-hospitalization duration of illness more than 7 days, presence of diabetes mellitus, serum creatinine (Scr) more than 1.5 mg/dL, serum bilirubin more than 3 mg/dL, systolic blood pressure below 90 mmHg, altered sensorium, and acute respiratory distress syndrome were associated with poor prognosis. **Conclusion:** A high degree of clinical suspicion is required for the early diagnosis of scrub typhus and the factors associated with poor prognosis must be considered to reduce morbidity and mortality.

Key words: Scrub typhus; Clinical profile; Prognostic factors

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i2.58401

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Scrub typhus is one of the causes of acute febrile illness caused by *Orientia tsutsugamushi*, an intracytosolic, Gram-negative rickettsial organism.[1] The vector for transmission of scrub typhus is mite, *Leptotrombidium pallidum*. The rickettsial organism persists in nature transovarially from one generation of mites to the next. Humans, the dead end of the host, are infected by the bite of the larval stage of mites (chigger) that harvest the bacteria in its salivary glands.[2]

Patient suffering from scrub typhus usually presents to the hospital with complaints of fever, chills, headache, and multiple systemic symptoms that need serious medical attention.[3] There may be multiorgan failure caused by vasculitis and perivascular inflammation resulting in vascular leakage and end-organ damage to the lungs, liver, and kidney.[4]

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Eschar is a pathognomonic finding for clinical diagnosis, which is a black necrotic skin with an erythematous border at the site of the chigger bite. The prevalence of Eschar is variable and it ranges from 7% to 80%. However, the absence of Eschar does not rule out scrub typhus infection.

Serology is the mainstay of diagnosis, and a significant titer of scrub typhus immunoglobulin M (IgM) antibody at the end of the 1st week is diagnostic.[5,6]

The signs and symptoms of scrub typhus infection closely resemble those of many other endemic causes of fever. Diagnosis is often missed clinically and tools for confirming diagnosis are not available in resource-poor health-care settings. Delay in diagnosis and starting proper treatment may lead to high morbidity and mortality. However, a high index of suspicion among clinicians and availability of diagnostic tests are necessary for the diagnosis and treatment of the disease which can be easily treated with antibiotic, doxycycline, and supportive care.

Although scrub typhus is a public health problem in India, it is burden and distribution is unclear due to lack of data and proper surveillance system.[7] In eastern India, there are few studies about scrub typhus infection and its clinical profile. So, this study was planned to address this issue.

Aims and objectives

This study aims to evaluate the clinical profiles, outcomes, and determine the factors associated with poor prognosis.

MATERIALS AND METHODS

This was an institutional-based cross-sectional study conducted over a period of 12 months from May, 2020, to April, 2021.

Sampling

All patients with fever attending general medicine outpatient department or emergency department of our institution were subjected to investigations to establish the cause of fever. Among them, 154 consecutively adult patients suffering from scrub typhus satisfying inclusion and exclusion criteria were selected for this study. Our institution is a Medical College Hospital situated in the southern part of West Bengal, India.

Inclusion criteria

The study included all patients aged 12 years and older who tested positive for scrub typhus using the InBios Scrub Typhus detect IgM enzyme-linked immunosorbent assay kit.

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study: Co-infection with other tropical infections such as malaria, dengue, typhoid, and chikungunya; patients undergoing treatment for tuberculosis and HIV; and patients who did not give their consent.

Tools and techniques

The study followed a structured approach for data collection, which included gathering demographic information and conducting clinical examinations using a pre-established form. In addition to this, a set of basic investigations was carried out, which encompassed a complete blood count, examination of a peripheral blood smear for malaria parasites, assessments of renal and liver functions, electrolyte levels, and coagulation profiles. Furthermore, all participants were screened for other prevalent febrile illnesses such as malaria, dengue, pneumonia, leptospirosis, typhoid fever, and chikungunya through appropriate diagnostic tests. Additional examinations such as chest X-rays, abdominal ultrasounds, blood cultures, computerized tomographic scans of the brain, and cerebrospinal fluid (CSF) analysis were conducted when clinically indicated.

The following criteria for different organ involvements were considered: (1) Pneumonitis was diagnosed in patients with acute onset cough, breathlessness with unilateral or bilateral alveolar or interstitial infiltrates on chest radiograph, and ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (PaO_2/FIO_2) >300 mmHg on arterial blood gas analysis, (2) acute respiratory distress syndrome (ARDS) was diagnosed if the patients presents with PaO_2/FiO_2 ratio ≤300 mmHg and/or low saturation with bilateral infiltrates on a chest radiograph in the absence of heart failure/cardiomegaly, (3) acute kidney injury was defined as rise of Scr of ≥0.3 mg/dL or 1.5–1.9 times baseline within a 24–48-h period or a reduction in urine output to <0.5 mL/kg/h for longer than 6 h, (4) hepatic dysfunction was diagnosed if the total bilirubin >1.5 mg/dL with elevation of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >40 IU/L, (5) meningoencephalitis was diagnosed as altered sensorium and signs of meningeal irritation associated with elevated protein and lymphocytic/neutrophilic cytology with normal or low sugar on CSF analysis, (6) pleural effusion was diagnosed if there was obliteration of costophrenic angle in chest radiograph, (7) shock was diagnosed as an arterial systolic blood pressure <90 mmHg and/or mean arterial pressure <65 mmHg requiring inotropes, and (8) multiorgan dysfunction syndrome (MODS) was defined as dysfunction of two or more organ systems.[8] Patients were treated with conservative management using oral or IV doxycycline. All other supportive measures such as blood transfusion, hemodialysis, ventilatory support, and inotropes were given as per indications.

Statistical analysis

At the end of the study, the data were analyzed using statistical software SPSS 19.0. Continuous variables were expressed in mean and standard deviations. Categorical variables were expressed as number and percentages.

Ethical issues

This study was done after proper ethical committee approval and informed consent was taken either from patient or a relative.

RESULTS

In the present study, maximum number of patients (26%) infected with scrub typhus were in the age group of 12–20 years. The mean age of the study population was 36.7±18.9 years. The male: female ratio was 1:1.48. The maximum number of patients were from the Hindu religion (66.2%) and with a higher secondary educational qualification (29.9%). The homemakers (32.5%) constitute the majority of patients in occupational group. Again, the majority of the patients came from small town (44.2%). Furthermore, the influx of patients was maximum in the months of July (22.1%) and November (22.1%) with 18.2% and 20.8% patients getting admitted in the months of September and October, respectively (Table 1).

Fever with chills was found in all patients. Headache, cough, nausea/vomiting, and yellow eyes/urine were present among 71.4%, 62.5%, 58.4%, and 26% of patients, respectively. Pallor, icterus, hepatomegaly, and splenomegaly were present among 19.5%, 28.6%, 20.1%, and 15.6% of patients, respectively. The pathognomonic feature of scrub typhus and Eschar was seen among only 13% of patients (Figure 1). Majority (75.3%) of the patients had 8–14 days of illness before hospitalization. The comorbid diseases such as diabetes mellitus and hypertension were seen only among 16.9% and 10.4% of patients, respectively (Table 2).

A major number of patients had hemoglobin level <10 g/dL (57.1%) and leukocyte count <4000/cumm (63.6%). Liver enzymes such as AST, ALT, and alkaline phosphatase were raised above normal range in 84.4%, 81.8%, and 75.3% of patients, respectively. Kidney function tests such as blood urea and Scr were above normal range among 51.9% and 57.1% of patients, respectively (Table 3).

Hepatic dysfunction was the most common complication (75.3%) in scrub typhus. Renal dysfunction, multiorgan dysfunction, meningoencephalitis, pneumonitis, and ARDS were some other complications found in 57.1%, 44.2%, 10.4%, 11.7%, and 7.8% of patients, respectively. The

Figure 1: Typical Eschar in a patient with scrub typhus

percentage of mortality among the patients was found to be 6.5 (Table 4).

The factors significantly linked with a negative prognosis, as indicated by a higher mortality rate, include male gender, pre-hospitalization illness duration exceeding 7 days, presence of diabetes mellitus, Scr levels exceeding 1.5 mg/dL, serum bilirubin levels surpassing 3 mg/dL, systolic blood pressure falling below 90 mmHg, altered sensorium, and the presence of ARDS (Table 5).

DISCUSSION

Scrub typhus is a re-emerging zoonotic bacterial infection primarily prevalent within the geographical region referred to as the "tsutsugamushi triangle." This area encompasses Japan in the northeast, far eastern Russia to the north, Pakistan in the northwest, and Northern Australia to the south.[9] The disease is endemic to the southeast Asian region and has an annual global incidence of 1 million reported cases.[10]

The name tsutsugamushi originated from Japan (tsutsuga means disease or illness and mushi means bug or insects). Approximately 1–3 weeks after being bitten by infected larval trombiculid mites (chiggers), individuals may experience symptoms characterized by a sudden onset of fever, headache, chills, arthralgia, myalgia, lymphadenopathy, maculopapular rash, and occasionally the formation of an Eschar at the site of the bite. Although most symptoms are mild, severe complications such as interstitial pneumonia, myocarditis, encephalitis, and multiorgan failure have been reported.[11] Rare complication such as cerebral venous sinus thrombosis is known to occur in scrub typhus.[12] It is one of the important causes of acute undifferentiated febrile illness in Asia.[13]

Table 1: Patient characteristics and epidemiological profile in patients with scrub typhus

Age distribution	Age group (years)	Number of patients (%)	Sex distribution	Sex	Number of patient (%)
	12–20	40 (26)		Male	62 (40.3)
	21–30	30 (19.5)		Female	92 (59.7)
	31–40	32 (20.8)		Male: Female	1:1.48
	41–50	14 (9.1)			
	51–60	16 (10.4)			
	61–70	12 (7.8)			
	>70	10 (6.5)			
	Mean age in years±standard deviation	36.7±18.9			
Religion	**Name of religion**	**Number of patients (%)**	**Education**	**Educational level**	**Number of patients (%)**
	Hinduism	102 (66.2)		Below primary level	10 (6.5)
	Muslim	38 (24.7)		Primary level	30 (19.5)
	Christianity	6 (3.9)		Secondary level	42 (27.3)
	Others	8 (5.2)		Higher secondary level	46 (29.9)
				Graduation and above	26 (16.9)
Occupation	**Occupational type**	**Number of patients (%)**	**Residence**	**Residential area type**	**Number of patients (%)**
	Farmer	28 (18.2)		Village	28 (18.2)
	Manual laborer	18 (11.7)		Small town	68 (44.2)
	Office worker	16 (10.4)		Big town or city	58 (37.7)
	Homemaker	50 (32.5)			
	Students	30 (19.5)			
	Retired	12 (7.8)			
Month wise distribution	**Month**	**Number of patients (%)**			
	May, 2020	2 (1.3)			
	June, 2020	12 (7.8)			
	July, 2020	34 (22.1)			
	August, 2020	6 (3.9)			
	September, 2020	28 (18.2)			
	October, 2020	32 (20.8)			
	November, 2020	34 (22.1)			
	December, 2020	0 (0)			
	January, 2020	0 (0)			
	February, 2020	2 (1.3)			
	March, 2020	0 (0)			
	April, 2020	4 (2.6)			

The majority of patients with scrub typhus were in the younger age group in the present study, which is similar to other studies.[14,15] This is explained traditionally by the more outdoor activity of young people and exposure to vector.

In our study, there is a notable predominance of females, accounting for 59.7%, a finding consistent with Bansod et al., (57.85%) and Palanivel et al.[14,15] However, Devasagayam et al., reported that both males and females are equally affected, with no significant gender-based difference observed.[7]

In this study, the majority of scrub typhus patients were homemaker. This conflicts with the findings of Devasagayam et al., who reported that individuals engaged in agriculture and unskilled labor were the primary groups affected by the disease.[7] The role of mite-ridden rodents or domesticated dogs in the transmission of organism in the indoor-bound person is the explanation for the findings of present study.[16] It transpires from the majority of the studies from India that the outbreak of scrub typhus is mainly in the post-monsoon season, from July to November, which is similar to our present study.[17-19] During this period, there is an increase in secondary shrub vegetation which in turn favors the growth of the vector. Moreover, farmers from the villages (18.2% in the present study) are also actively involved in harvesting during this season and are exposed to bite of larval mites.[19-21] It may be stated that general health education of farmers with simple measures such as use of full-sleeve dresses, daily washing of used clothes, and avoidance of open-air defecation will certainly reduce the transmission of the disease.

Table 2: Clinical profile in patients with scrub typhus

Symptoms	Presenting complaints	Number of patients (%)
	Fever with chills	154 (100)
	Cough	104 (62.5)
	Breathlessness	34 (22.1)
	Nausea/vomiting	90 (58.4)
	Headache	110 (71.4)
	Yellow eyes/urine	40 (26)
	Altered sensorium	22 (14.3)
	Decreased urine output	34 (22.1)
Signs	**Physical examination findings**	**Number of patients (%)**
	Pallor	30 (19.5)
	Icterus	44 (28.6)
	Hypotension/shock	24 (15.6)
	Hepatomegaly	32 (20.1)
	Splenomegaly	24 (15.6)
	Eschar	20 (13)
	Meningeal sign	16 (10.4)
Pre-hospital duration of illness	**Duration of illness**	**Number of patients (%)**
	≤7 days	32 (20.8)
	8–14 days	116 (75.3)
	>14 days	6 (3.9)
Comorbidities	**Comorbid disease**	**Number of patients (%)**
	Diabetes mellitus	26 (16.9)
	Hypertension	16 (10.4)
	*COPD/bronchial asthma	8 (5.2)
	Chronic renal failure	2 (1.3)

*COPD: Chronic obstructive pulmonary disease

Table 3: Basic laboratory profile in patients with scrub typhus

Laboratory test parameters	Number of patients (%)	Reference values of the parameter
Hemoglobin <10 g/dL	88 (57.1)	Male: 14–18 g/dL Female: 12–16 g/dL
Leukocyte count <4000 cells/cumm	98 (63.6)	4000–11000 cells/cumm
Leukocyte count >10000 cells/cumm	30 (19.5)	4000–11000 cells/cumm
Platelet count <150000/µL	74 (48.1)	150000–450000/µL
Serum bilirubin >3 mg/dL	38 (24.7)	0.1–1.2 mg/dL
$^{+}$AST >40 IU/L	130 (84.4)	≤40 IU/L
$^{++}$ALT >40 IU/L	126 (81.8)	≤40 IU/L
$^{\#}$ALP >130 IU/L	116 (75.3)	≤130 IU/L
Blood urea >40 mg/dl	80 (51.9)	17–43 mg/dL
Serum creatinine >1.5 mg/dL	88 (57.1)	Male: 0.7–1.3 mg/dL Female: 0.6–1.1mg/dL

$^{+}$AST: Aspartate aminotransferase, $^{++}$ALT: Alanine aminotransferase, $^{\#}$ALP: Alkaline phosphatase

Table 4: Complications and final outcome in patients with scrub typhus

Complications	Number of patients (%)
Hepatic dysfunction	116 (75.3)
Acute kidney injury	88 (57.1)
Multi-organ dysfunction syndrome	68 (44.2)
Meningoencephalitis	16 (10.4)
Shock	24 (15.6)
Pneumonitis	18 (11.7)
Pleural effusion	8 (5.2)
ARDS	12 (7.8)
Outcome	
Survived	144 (93.5)
Dead	10 (6.5)

ARDS: Acute respiratory distress syndrome

The present study strengthens the fact that scrub typhus commonly presents with non-specific symptoms such as acute onset fever, along with myalgia, headache, cough, nausea, vomiting, and other general complaints. The similar clinical presentation in other common diseases such as malaria, dengue fever, and typhoid fever creates difficulties in the clinical diagnosis of scrub typhus. Therefore, a high index of clinical suspicion and an intense search for Eschar are essential for the proper diagnosis of scrub typhus[22,23] (Figure 1). Similar to our study, the positivity rate of Eschar (13%) is lower in some earlier studies.[19,23] This may be explained by past exposure to infecting organism in the past or infection with a variable

Table 5: Factors associated with poor prognosis in patients with scrub typhus

Indicators	Survived (Number of patients/total number of patients)	Dead (Number of patients/total number of patients)	P-value
Age >60 years	24/144	2/10	0.785545
Male sex	54/144	8/10	0.00805
Female sex	90/144	2/10	
Pre-hospital duration of illness <7 days	22/144	0/10	<0.001
Pre-hospital duration of illness 8–14 days	122/144	4/10	
Pre-hospital duration of illness >14 days	0/144	6/10	
Diabetes mellitus	22/144	4/10	0.043583
Hypertension	16/144	0/10	0.265483
COPD/asthma	8/144	0/10	0.443971
Hemoglobin <10 g/dL	80/144	8/10	0.130927
Serum creatinine >1.5 mg/dL	78/144	10/10	0.004624
Serum bilirubin >3 mg/dL	28/144	10/10	<0.001
Shock (systolic blood pressure <90 mmHg)	14/144	10/10	<0.001
Altered sensorium	14/144	8/10	<0.001
ARDS	2/144	10/10	<0.001

ARDS: Acute respiratory distress syndrome, COPD: Chronic obstructive pulmonary disease

strain. Hence, the mere absence of Eschar does not rule out the diagnosis of scrub typhus.

Several studies in the past similar to ours indicate that systemic complications are frequent findings in scrub typhus.[24,25] *O. tsutsugamushi* has more than 20 antigenically distinct serotypes and some strains seem to have higher virulence.[26] The complications in scrub typhus develop after the 1st week of illness.[14] In addition to the lack of specific clinical findings, the antibodies in scrub typhus do not reach detectable levels for 5–10 days after disease onset, and laboratory diagnosis in the early part of the illness is very difficult. Hence, the chances of complications are higher.

The specimen of choice, which is a biopsy of the Eschar and/or rash, is unfortunately rarely obtained, though the level of orientia DNA is in abundance, remains unaffected by prior antibiotic treatment, and persists in the lesion throughout its duration.[27]

The most common complication in our study was hepatic dysfunction (75.3%) which is similar to the findings by Narvencar et al.[28] Earlier studies from India had reported meningoencephalitis as a complication in the range of 9.5–23.3%.[24,29] In the present study, 10.4% of the patients with scrub typhus had meningoencephalitis. Scrub typhus should be considered in the differential diagnosis of meningoencephalitis. The case fatality rate in our study was 6.5% which is similar to the result of Devasagayam et al., (6.3%) and Sharma et al., (5.15%).[7,22] There is a decreasing trend in case fatality in scrub typhus during recent years.[25,30] The decreasing mortality can be attributed to increased awareness, timely initiation of antibiotic treatment, and the presence of less virulent strains of the organism.

Bansod et al., found that early presentation of the disease with duration of fever <7 days has better prognosis which is similar to our study.[14] Systemic complications such as acute renal failure, hypotension, meningoencephalitis, ARDS, and MODS were associated with poor prognosis in many previous studies, similar to ours.[25,31,32]

Limitations of the study

The hospital-based study rather than a population based study and a meager number of patients are the limitation of this study.

CONCLUSION

It can be concluded from this study that younger, female, and homemakers were more sufferers of scrub typhus. The post-monsoon season from July to November was the peak time of infection. Clinically, Eschar in patients with short-duration fever is diagnostic of scrub typhus but is seen in only 13% of patients. The incidence of scrub typhus complications was found to be high in the southern part of West Bengal, hepatic dysfunction being the most common. The case fatality rate in scrub typhus was 6.5%. The male sex, pre-hospitalization duration of illness more than 7 days, presence of diabetes mellitus, Scr more than 1.5 mg/dL, serum bilirubin more than 3 mg/dL, systolic blood pressure below 90 mmHg, altered sensorium, and ARDS were associated with poor prognosis. A high degree of clinical suspicion is required for early diagnosis of scrub typhus and the factors associated with poor prognosis must be considered to reduce morbidity and mortality.

ACKNOWLEDGMENTS

Authors are thankful to all patients and their relatives who participated in this study.

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Source of Support: Nil, **Conflicts of Interest:** None declared.