

Establishing the role of Demographic, Clinical and Laboratory Parameters in Scrub typhus patients from a tertiary care centre

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Abstract

Background: Scrub typhus (ST) is one of the common Rickettsial diseases caused by an obligate intracellular bacterium, *Orientia tsutsugamushi* (Orientia). It is transmitted to humans by bite of larval mites or chiggers of *Leptotrombidium* group, which usually feed on the wild rats of the subgenus *Rattus*. The disease generally presents as acute febrile with symptoms like fever, headache, eschar, myalgia, maculopapular rash, lymphadenopathy, breathlessness, cough, nausea, vomiting, and coagulopathies that can result in circulatory system collapse. Serological tests still remains the main stay for the diagnosis of scrub typhus. Doxycycline is the preferred drug in the treatment of scrub typhus. **Materials and methods:** A total of 40 confirmed cases of scrub typhus by IgM ELISA were studied. The blood samples collected from subjected to processing for detection of specific IgM antibodies against the causative agent *Orientia tsutsugamushi* by ELISA method. Other relevant investigations which are required for diagnosis were also performed. **Result:** Out of 40 cases diagnosed of scrub typhus with positive serology for IgM ELISA, 21 cases were female and 19 were male. Maximum cases belonged to 50-59 years age group, 31 cases were from rural areas with 37 cases reported in farmers or agriculture workers. The common symptoms of these patients include fever, weakness and myalgia. The frequent signs noted in these patients include eschar, lymphadenopathy, and hypotension. The common abnormal laboratory parameters observed in these patients include thrombocytopenia, increased transaminase and leucocytosis. **Conclusion:** As scrub typhus is endemic in many parts of India, a high index of clinical suspicion is required for diagnosis of scrub typhus due to varied clinical presentations, non specific blood parameters and lack of highly sensitive and specific diagnostic tests, especially in rural areas. Serological tests still remains the main stay for the diagnosis of scrub typhus. Doxycycline remains the antibiotic of choice for treatment of scrub typhus.

Keywords: Doxycycline; ELISA; Eschar; Rickettsial diseases; Scrub typhus.

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Introduction

Scrub typhus (ST) is one of the common Rickettsial diseases caused by an obligate intracellular bacterium, *Orientia tsutsugamushi* (Orientia)[1]. It is transmitted to humans by bite of larval mites or chiggers of *Leptotrombidium* group, which usually feed on the wild rats of the subgenus *Rattus*. Man is infected accidentally when he encroaches the mite-infested areas[2]. The disease generally presents as acute febrile with symptoms like fever, headache, eschar, myalgia, maculopapular rash, lymphadenopathy, breathlessness, cough, nausea, vomiting, and coagulopathies that can result in circulatory system collapse[1-4]. The incubation period of scrub typhus is about 5 to 20 days (median, 10-12 days)[5]. World Health Organization (WHO) identifies scrub typhus as a re-emerging disease in South-East Asia and the South-Western Pacific region with a case fatality rate of up to 30% in untreated cases and stresses the need for its surveillance and has recently been identified as one of the important neglected zoonoses of public health importance[6,7]. The diagnosis of scrub typhus is difficult as patients often come to hospital with

undifferentiated fever and symptoms that are similar to other endemic infections such as leptospirosis, malaria and dengue[8]. The presence of the pathognomonic eschar, the painless ulcer with black necrotic centre at the site of mite inoculation, can help in establishing clinical diagnosis however, its presence in patients varies widely (7%-97%)[9,10]. Other nonspecific parameters like elevated levels of CRP and LDH, an indication of hepatic dysfunction and inflammation, were observed in more than 90% of the patients. Elevated levels of AST and ALT were found in approximately 80% of the patients[11]. Laboratory tests for scrub typhus often have limited diagnostic accuracy and are generally in limited supply in resource limited or outpatient settings. Various diagnostic tests like Weil Felix test, immunofluorescent assay (IFA), immunoperoxidase test (IIP) and enzyme linked immunosorbent assay (ELISA) were employed for detecting scrub typhus with advantages and limitations for each method. Molecular detection methods, including using the polymerase chain reaction (PCR) to detect various genes targets have also been developed, however they have limitations in terms of diagnostic sensitivity due to the limited period of rickettsaemia[12]. Failure of timely diagnosis leads to significant morbidity and mortality, with timely diagnosis treatment is easy, affordable and often successful with dramatic response to antimicrobials. As antimicrobials effective for rickettsial diseases are usually not included in empirical therapy of nonspecific febrile illnesses,

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treatment of rickettsial diseases is not provided unless they are suspected[13].The aim of present study is to establish correlation between clinical manifestations, laboratory findings and treatment outcomes of scrub typhus patients in a tertiary care setting, which provide inputs for physicians practicing in endemic areas with limited resources.

Materials and methods

Present study was conducted from March 2020 - October 2020 in the department of general medicine of a large teaching tertiary care institution. A total of 40 confirmed cases of scrub typhus by IgM ELISA were studied.

Inclusion criteria

1. Positive serology for scrub typhus.

Exclusion criteria

1. Patients with other established causes of pyrexia, such as malaria, dengue, leptospirosis, enteric fever, and viral meningitis

2. Negative serology for scrub typhus

3. Incomplete case records

4. Patient refusal to participate in the study.

The blood samples collected from subjected to processing for detection of specific IgM antibodies against the causative agent *Orientia tsutsugamushi* by ELISA method. The patients having IgM

antibodies against *Orientia tsutsugamushi* in their serum were diagnosed as having scrub typhus. Records of these cases pertinent to demographic and clinical information including age, gender, occupation, presenting features, examination findings, laboratory results, complications, treatment instituted were collected. Other relevant investigations such as complete blood count including platelet count, serum electrolytes, urine analysis, renal function tests (Urea and Creatinine), liver function tests, smear and rapid antigen tests for malaria parasite, serology for leptospirosis (IgM) serology for dengue (NS1 antigen or IgM as applicable), serology for chikungunya (IgM), Widal test were also performed. The patients also underwent ultrasonography of abdomen, chest X-ray, CT scan of brain and CSF study as and when necessary. This study was conducted after clearance from the institutional ethics committee.

Results

Out of 40 cases diagnosed of scrub typhus with positive serology for IgM ELISA, 21(52.5%) were female and 19(47.5%) were male. Maximum cases belonged to 50-59 years age group (9 cases) and the youngest case was reported in 16 years and oldest in 70 years (Table 1). Of 40 cases, 31 (77.5%) cases were from rural areas with 37 (92.5%) cases reported in farmers or agriculture workers (Table 2&3).

Table 1: Age and sex distribution of cases

Age Group	Male	Female
10-19	2	4
20-29	2	4
30-39	3	3
40-49	1	2
50-59	3	6
60-69	5	1
70-79	3	1
Total	19	21

Table 2: Area wise distribution of cases

Residence	No. of patients
Rural	31
Semi-urban	04
Urban	05

Table 3: Distribution of cases on occupation

Occupation	No. of patients
Farmer/Agriculture worker	37
Others	03

The common symptoms of these patients include fever in 40(100%) cases, weakness in 32(80%) cases, and myalgia in 24(60%) cases followed by headache in 20 cases, nausea and vomiting in 16 cases, rash in 12 cases, cough in 8 cases and breathlessness in 4 cases (Table 4).

Table 4: Showing the common presenting symptoms

Symptoms	No. of Patients Presented
Fever	40
Weakness	32
Myalgia	24
Headache	20
Nausea and Vomiting	16
Rash	12
Cough	08
Breathlessness	04

The frequent signs noted in these patients include eschar in 28(70%) cases (Figure 1), lymphadenopathy in 12(30%) cases, and hypotension in 8 (20%) cases followed by icterus in 6 cases pedal edema in 2 cases (Table 5).

Table 5: Showing the common presenting signs

Signs	No. of Patients Presented
Eschar	28
Lymphadenopathy	12
Hypotension	08
Icterus	06
Pedal edema	02



Fig 1: Picture showing the eschar in patient with Scrub typhus

The common abnormal laboratory parameters observed in these patients include thrombocytopenia and increased transaminase in 32(80%) cases each; and leucocytosis in 22(55%) cases followed by leucocytopenia in 18 cases, anemia in 12 cases with increased urea/creatinine and increased bilirubin in 2 cases each (Table 6).

Table 6: Abnormal blood parameters

Investigation	No. of Patients Presented
Thrombocytopenia	32
Increased Transaminase	32
Leucocytosis	22
Leucocytopenia	18
Anemia	12
Increased Urea/Creatinine	02
Increased Bilirubin	02

All the patients were administered with Doxycycline 100 mg twice daily for 10 to 14 days along with supportive management. All the patients were cured with this therapy.

Discussion

Scrub typhus is the most common zoonotic rickettsial infection in the Indian subcontinent, caused after the bite of a trombiculid mite larva carrying *Orientia tsutsugamushi*[14]. Scrub typhus infection is an important cause of acute undifferentiated fever in South East Asia. The clinical picture is characterized by sudden onset fever with chills and non-specific symptoms that include headache, myalgia, sweating and vomiting[15]. In our study, 21 cases were seen in female and 19

cases seen in males with slight female predominance, which was in concordance with study done by Pathania et al[14] and Takhar et al[16]. Most of the cases in our study was observed in rural population with 31 (77.5%) cases which was in concordance with Bibhuti et al[5] Pathania et al[14] and Takhar et al[16]. The common symptoms in our study include fever in 40(100%) cases, weakness in 32(80%) cases, and myalgia in 24(60%) cases followed by headache in 20 cases, nausea and vomiting in 16 cases, rash in 12 cases, cough in 8 cases and breathlessness in 4 cases, which was observed in most of the studies (Table 7), thus indicating fever as the consistent feature in scrub typhus infection.

Table 7: Comparison of symptoms in various studies

Symptoms	Bibhuti et al[5]	Vivekanandan et al[2]	Takhar et al[16]	Pathania et al[14]	Our study
Fever	14	50	66	54	40
Myalgia/weakness	5	19	20	40	32
Headache	6	26	22	45	20
Nausea/ Vomiting	5	29	18	29	16
Cough	NA	20	32	28	8

The frequent signs noted in our study are eschar in 28(70%) cases, lymphadenopathy in 12(30%) cases, and hypotension in 8 (20%) cases followed by icterus in 6 cases pedal edema in 2 cases. There was considerable discordance regarding the signs seen in scrub typhus among various studies like eschar was common sign in our study where as hypotension was frequent sign in Bibhuti et al[5] and pedal edema was common sign seen in study by Takhar et al[6]. This shows that even though eschar is characteristic of this disease it

shows wide variability, this may be due to variability in the infecting serotype in different regions, high skin color in the Indian subcontinent, and high rates of under detection due to the painless and non itchy characteristics of the eschar[14]. Eschar, the pathognomic feature of scrub typhus can develop in various sites like abdomen, nape of neck, groin and axilla. Some studies have suggested that the presence of generalized lymphadenopathy suggests a late presentation and a worse outcome[16].

Table 8: Comparison of signs among various studies

Signs	Bibhuti et al[5]	Takhar et al[16]	Our study
Eschar	3	08	28
Lymphadenopathy	3	12	12
Hypotension	13	20	8
Pedal edema	4	42	2
Icterus	NA	33	6

The common abnormal laboratory parameters observed in our study include thrombocytopenia 32(80%) case, which was also the common abnormality in Takhar et al[16] in our study increased transaminase is seen in 32(80%) cases, which was in concordance with study done by Vivekanandan et al[2]. Other abnormalities noted in our study include leucocytosis in 22(55%) cases, leucocytopenia in 18 cases, anemia in 12 cases with increased urea/creatinine and increased bilirubin in 2 cases each, these were also the frequently observed abnormal parameters in various studies.

Table 9: Comparison of various blood parameters in different studies

Lab Investigation	Bibhuti et al[5]	Vivekanandan et al[2]	Takhar et al[16]	Pathania et al[4]	Our study
Thrombocytopenia	1	5	52	7	32
Increased transaminases	14	47	32	40	32
Leukocytosis	5	15	20	16	22
Leukopenia	NA	1	10	1	18
Increased Creatinine	1	6	34	2	2

In view of low index of suspicion, non-specific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests, these infections are notoriously difficult to diagnose. Serological tests still remains the main stay for the diagnosis of scrub typhus though elevated liver enzymes might give a clue. Serological test which has been widely used in India for diagnosis of scrub typhus is the Weil Felix test for it is easily available and highly specific; however it lacks sensitivity[17]. In our study the diagnosis was done by detection of IgM antibody specific for scrub typhus by ELISA method. In our study, serotyping and genotyping were not performed due a lack of resources. Severity of illness is due to multiple factors like virulence of the infecting strain, host factors and nutritional status. Several complications like CNS involvement, pulmonary involvement and renal impairment was infrequent observed in various studies, in our study such complications were rare attributable to early diagnosis and treatment. None of the cases in the series required intensive care unit (ICU) care. Doxycycline is the preferred drug in the treatment of scrub typhus. It is so much effective in treating the disease such that therapeutic response to doxycycline test therapy is used as a diagnostic test. All patients in our study were administered doxycycline and responded well. All the patients were administered with doxycycline 100 mg twice daily for 10 to 14 days depending on the clinical improvement along with supportive management. Average duration of hospital stay for these patients was 6-7 days in our study. All patients were discharge without any complications.

Conclusion

As scrub typhus is endemic in many parts of India, a high index of clinical suspicion is required for diagnosis of scrub typhus due to varied clinical presentations, non specific blood parameters and lack of highly sensitive and specific diagnostic tests, especially in rural areas. Since the clinical spectrum of disease ranges from acute febrile illness to serious complications, early diagnosis and treatment helps in reducing significant mortality and morbidity. Serological tests still remains the main stay for the diagnosis of scrub typhus in areas with limited recourses. Doxycycline remains the antibiotic of choice for treatment of scrub typhus. An empirical therapy with doxycycline should be started if there is high index of suspicion as early diagnosis and timely antibiotic therapy may prevent further complications.

References

- Chao CC, Belinskaya T, Zhang Z, Jiang L, Ching WM. Assessment of a Sensitive qPCR Assay Targeting a Multiple-Copy Gene to Detect *Orientia tsutsugamushi* DNA. *Trop Med Infect Dis.* 2019;4(3):113.
- Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. *J Assoc Physicians India.* 2010;58:24-28.
- Phongmany S, Rolain JM, Phetsouvanh R, Blacksell SD, Soukhaseum V, Rasachack B, et al. Rickettsial infections and fever, Vientiane, Laos. *Emerg Infect Dis.* 2006;12(2):256-62.
- Kasper MR, Blair PJ, Touch S, Sokhal B, Yasuda CY, Williams M, et al. Infectious etiologies of acute febrile illness among patients seeking health care in south-central Cambodia. *Am J Trop Med Hyg.* 2012 Feb;86(2):246-253.
- Saha B, Chatterji S, Mitra K, Ghosh S, Naskar A, Ghosh MK, et al. Socio-demographic and Clinico-Epidemiological Study of Scrub Typhus in Two Tertiary Care Hospitals of Kolkata. *J Assoc Physicians India.* 2018 May;66(5):22-5.
- Kumar V, Kumar V, Yadav AK, Iyengar S, Bhalla A, Sharma N, et al. Scrub typhus is an under-recognized cause of acute febrile illness with acute kidney injury in India. *PLoS Negl Trop Dis.* 2014;8(1):e2605.
- John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. *Lancet.* 2011;377(9761):252-269.
- Lim C, Paris DH, Blacksell SD, Laongnualpanich A, Kantipong P, Chierakul W, et al. How to determine the accuracy of an alternative diagnostic test when it is actually better than the reference tests: a reevaluation of diagnostic tests for scrub typhus using bayesian LCMs. *PLoS One.* 2015; 10(5): e0114930.
- Silpapojakul K, Varachit B, Silpapojakul K. Paediatric scrub typhus in Thailand: a study of 73 confirmed cases. *Trans R Soc Trop Med Hyg.* 2004;98(6):354-359.
- Paris D, Day NP. Tropical rickettsial infections. In: Farrar J, Hotez P, Junghans T, Kang G, Lalloo D, White N, editors. *Manson's Tropical Diseases.* Philadelphia: Elsevier Saunders; 2014:273-291.
- Ogawa M, Hagiwara T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y, et al. Scrub typhus in Japan: epidemiology and clinical features of cases reported in 1998. *Am J Trop Med Hyg.* 2002; 67(2): 162-165.
- Saraswati K, Day NPJ, Mukaka M, Blacksell SD. Scrub typhus point-of-care testing: A systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2018;12(3):e0006330.
- Ramyasree A, Kalawat U, Rani ND, Chaudhury A. Seroprevalence of Scrub typhus at a tertiary care hospital in Andhra Pradesh. *Indian J Med Microbiol.* 2015;33(1):68-72.
- Pathania M, Amisha, Malik P, Rathaur VK. Scrub typhus: Overview of demographic variables, clinical profile, and diagnostic issues in the sub-Himalayan region of India and its comparison to other Indian and Asian studies. *J Family Med Prim Care.* 2019;8(3):1189-1195.
- Peter JV, Sudarsan TI, Prakash JA, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. *World J Crit Care Med.* 2015 ;4(3):244-50.
- Takhar RP, Bunkar ML, Arya S, Mirdha N, Mohd A. Scrub typhus: A prospective, observational study during an outbreak in Rajasthan, India. *Natl Med J India.* 2017;30(2) 69-72.
- K SM, Rajendran A. Scrub Typhus in Adults – A Case Series from a Tertiary Care Hospital. *International Journal of Medicine and Public Health.* 2011;1(2):34-46.

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