

Scrub Typhus - Changing Trends and Varying Symptomatology

Lizy Mathew¹, Ragi R.G²

¹Associate Professor, Department of Microbiology, Government Medical College, Thiruvananthapuram.

²Assistant Professor, Department of Microbiology, Government Medical College, Thiruvananthapuram.

Corresponding Author: Lizy Mathew

ABSTRACT

Background: Cases of scrub typhus are reported in increasing numbers in various parts of Kerala. The varying symptomatology and clinical presentations and complications have made the diagnosis difficult without laboratory support.

Aim: This descriptive study attempts to analyse the symptomatology and complications in patients admitted with Scrub typhus during 2015 and 2016 and to estimate the seroprevalence of Scrub typhus in the hospital during this period.

Methods: Forty inpatients who were tested positive for Scrub typhus IgM ELISA were included in the study. The clinical records were examined in detail for symptoms, signs and complications. The serum samples were also subjected to Weil Felix test. Seroprevalence was estimated from laboratory records.

Results: Fever (100%) and myalgia (42.5%) were the common symptoms but rare symptoms like bleeding manifestations, jaundice and loose stools were seen in 10% each. Eschar was present in 20% patients. Complications like acute kidney injury (15%), myocarditis (5%) and ARDS (2.5%) were found. Nineteen patients gave a positive Weil Felix test i.e. (47.5%).

Conclusion: Scrub typhus is occurring with increasing prevalence and varying clinical presentations. Weil Felix test can still be employed in resource poor settings like primary health care facilities where even ELISA is not feasible.

Key words: scrub typhus, Weil-Felix test

INTRODUCTION

Among zoonotic diseases that continue to plague mankind, scrub typhus is becoming more prominent especially in our part of the world. Scrub typhus also known as *tsutsugamushi disease* is caused by a small gram negative obligate intracellular organism *Orientia tsutsugamushi* belonging to the family Rickettsiaceae. It was first observed in Japan in 1999.¹ Its polysaccharides bear an antigenic relationship to proteus OX-K, which is thus used in serologic tests to confirm scrub typhus. The occurrence of the serotypes varies in different countries. Major serotypes are - Karp, Kawasaki, Kato, Gilliam, Boryong. New serotypes of Shimokoshi, Kuroki have been reported from various parts of Japan. The organism is mainly transmitted by the bite of larvae (chiggers) of the trombiculid mite belonging to the Leptotrombidium. The common species are *L.akamushi* and *L.deliense*. The species found in India is *L.deliense*. Chiggers attach firmly to the surface of the host with the mouth parts sucking up liquid tissue and transmitting the pathogen.

Lifecycle of *Leptotrombidium* consists of egg, larvae, nymph and adult. Transovarial and transstadial transmission are the main mechanisms for maintaining the organism in nature. Transstadial means from one stage to the next and transovarial is from the female to the offspring. Adult and nymph are free living in the soil. Only chiggers which are only 0.2 mm can

transmit the disease to humans and other vertebrates.

Scrub typhus is endemic to a part of the world known as the “tsutsugamushi triangle.” This extends from Japan, Taiwan, China, South Korea,² Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales³.

In India, the presence of scrub typhus has been known for several years. During World War II, there was an outbreak of this disease in Assam and West Bengal, in the 1965 Indo-Pak war and - in a unit of an army deployed at the Pakistan border of India. The disease is widely spread all over the country- Jammu and Kashmir, Himachal Pradesh, Uttaranchal, West Bengal, Assam, Maharashtra, Kerala and Tamilnadu.⁴The animal reservoirs, scrub vegetation and suitable climatic conditions have played a major role in the increased incidence of Scrub typhus in Kerala. Although enough statistical data about scrub typhus in Kerala are not available in the public domain, a few publications have come out.

Objectives:

1. This study aims at bringing out the varying symptomatology, atypical presentations and other laboratory findings associated with the disease, because rare presentations make the diagnosis of scrub typhus difficult without laboratory support.
2. To estimate the seroprevalence of the disease from laboratory records.

Study design: Cross sectional study the patients with AFI (Acute febrile illness) whose serum samples were positive for IgM scrub typhus were included in the study.

Study setting: Department of General Medicine and Department of Microbiology, Government Medical College Thiruvananthapuram. The hospital is a tertiary care center that caters to the three districts of Thiruvananthapuram, Kollam and Pathanamthitta. Most of the cases with

diagnostic difficulties were referred to our hospital.

METHODS

The prevalence of scrub typhus among patients with AFI was also estimated by reviewing the laboratory records. The serum samples positive for IgM Dengue and IgM Leptospira & cases of malaria were excluded. A total number of 40 serologically confirmed cases of Scrub typhus during 2015 & 2016 who were admitted in the ward for more than one week were studied in detail. The study was submitted to the Institutional Research Committee and was cleared by the Institutional Ethics Committee.

The ELISA was performed on these patient samples using Inbios International ELISA Kit. The positive serum samples were stored in SV2 vials in deep freezer for doing Weil Felix test (FAR srl). Weil Felix test was done in test tubes as per the kit literature. The patient details, clinical features and laboratory findings were recorded on a proforma. The patients were followed up and outcome analysed.

RESULTS & DISCUSSION

Cases of scrub typhus were detected throughout the year but there were some clustering of cases in the post monsoon period following the north east and southwest monsoons. Kerala has two monsoon seasons, southwest monsoon that arrives by May end or June and north east monsoon that arrives in October and continues till December. Similar post monsoon surges were reported by other authors.^{5,6} In the immediate post monsoon period there is an overgrowth of secondary scrub vegetation, which is the habitat for trombiculid mites in mite islands.⁷In a review of global epidemiology of scrub typhus by Guang et al it is mentioned that occurrence of scrub typhus varies with season.⁸

The following diagram shows the prevalence rates from laboratory records.

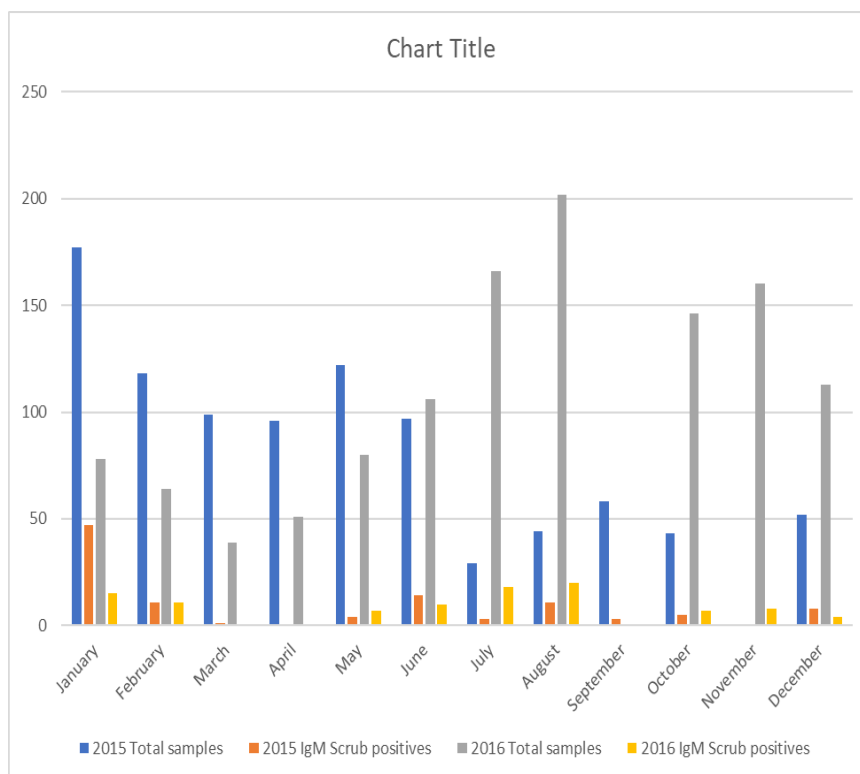


Diagram 1.-Seroprevalence of scrub typhus in 2015 & 2016

Table 1: Patient Characteristics

Age	Frequency	Male	Female
< 20	4	3	1
20-39	11	4	7
40-59	19	11	8
≥ 60	6	5	1

Among the forty cases 57.5% were males and 42.5% were females. Male predilection for the disease has been reported in other studies also. Kedareshwar has analysed 44 cases of AFI and out of the positives, five were males and ten were females⁹. Seventy five percent of patients belonged to the age ranging from 20-59 yrs because they were more involved in outdoor activities.

A study from Thailand showed no difference in distribution of cases between the two genders¹⁰. Probably the sex predilection for the disease is dependent on the cultural characteristics and the living patterns of the population. Majority of the patients belonged to 40 – 59 yrs. age group (47.5%), which included 11 males (58%) and 8 females (42 %) followed by 20-39 yrs age (27.5%). Extremes of age constituted 25% which included more than 60 yrs (15%) and less than 20 yrs (10%). Youngest

patient was 13-year-old female and the oldest was 83 yrs old male.

Duration of Fever at the time of Admission	No. of cases N= 40
Fever ≤ 7 days	26(65%)
Fever >7 days & ≤ 14 days	9(22.5%)
Fever >14 days & ≤ 21 days	3(7.5%)
Fever > 21 days	2(5%)

The patients presented to the hospital after varying periods of fever. Even though our hospital is a tertiary care centre, some cases have reported early to the hospital with a history of 3 days fever. The time of presentation to the hospital is analysed in detail in the following table. The mean duration of fever prior to the presentation was 10.2 days.

Majority of patients (82%) were from the outskirts of Thiruvananthapuram district, which are rural or suburban areas. Six patients were from nearby district of Kollam and one from Pathanamthitta.

Table 2. Analysis of common symptoms

Symptom	Frequency	Percentage
Fever	40	100.0%
Chills	17	42.5%
Myalgia	17	42.5%
Eschar	8	20.0%
Cough	6	15.0%

Vomiting	6	15.0%
Abdominal pain	6	15.0%
Dyspnoea	5	12.5%
Icterus	4	10.0%
Headache	4	10.0%
Arthralgia	3	7.5%
Bleeding	3	7.5%
Loose stools	3	7.5%
Nausea	2	5%
Abnormal speech	1	2.5%
Chest Pain	1	2.5%

Government Medical College Thiruvananthapuram is a tertiary care centre. Hence only referred cases are admitted in our hospital.

Fever was associated with chills and myalgia in 42.5% of patients whereas other symptoms occurred with varying frequency.

Symptom combinations	N (%)
Fever +chills	17(42.5%)
Fever +chills+ myalgia	17(42.5%)
Fever+ myalgia+ arthralgia+ vomiting	6(15%)
Fever+ abdominal pain	5(12.5%)
Fever +loose stools	4 (10%)
Fever+ abdominal pain+ nausea	2(5%)

The predominant symptoms observed in the study were fever (100.0%), chills and myalgia (42.5%). Respiratory symptoms like cough and dyspnoea were present in 22.5% of patients.

Symptoms like bleeding manifestations, jaundice, and loose stools were present in 7.5%, 10% and 7.5% of patients respectively. Arthralgia in 7.5% abdominal pain was in 15% of patients. Rare symptoms like altered sensorium were noted in the 83 yr old man and abnormal speech was present in a young male patient each. Rare symptoms like deafness, dysarthria, and dysphagia have been documented but are usually transient, although deafness can last for several months.¹

Gastrointestinal symptoms and signs like nausea; vomiting and loose stools were present in 13 patients (32.5%). These symptoms could be used as a pointer to clinically suspect cases of scrub typhus and differentiate them from dengue and leptospira. A study by Kim et al mentions that unusual presentation of acute abdomen can also occur in patients from

hyperendemic areas¹¹. Kim et al observed that 22.7% of patients with diagnosed scrub typhus have gastrointestinal manifestations usually abdominal pain or tenderness, indigestion, nausea, vomiting, hematemesis, melena, and diarrhoea. Other reported gastrointestinal manifestations include granulomatous hepatitis, acalculous cholecystitis, pancreatic abscess and gastrointestinal bleeding^{12,13}.

The pathognomonic feature of scrub typhus is the presence of eschar. Eschar is a necrotic lesion of the skin at the site of chigger bite. It is a pathognomonic finding in the diagnosis of scrub typhus. Eschar was present in eight patients which comprised 20%. Common sites were chest, abdomen, shoulder, umbilicus, external genitalia etc. In an analysis of 50 cases of scrub typhus in Pondicherry, eschar was seen in 46% cases and the common sites were axilla, breast and groin. Eschar was not present in any of the patients as reported by Kedareshwar et al and Remyasree et al. whereas Varghese et al in his study reported that eschar was found in 55% of the patients. According to some reports the rate of eschar formation varies and is much less in the Indian subcontinent¹⁸ and could be due to the different virulence, load of the pathogen and host immunity.

No history of skin rashes has been reported in any of the 40 patients. The prevalence rate has been reported varying from 8.9% to 90% by different authors.²¹

Three patients (7.5%) had bleeding manifestations like bleeding per rectum, bleeding per vaginum, and haematuria probably as a result of thrombocytopenia. Bleeding manifestations were not recorded in most of the studies.

Clinical and Laboratory findings

Thrombocytopenia was present in 20% of patients. Leucocytosis was a predominant finding present in 37.5% of patients whereas leucopenia was present in 5% only. Other findings included hepatomegaly in 37.5%, elevated liver enzymes (alkaline phosphatase, alanine

aminotransferase and aspartate aminotransferase indicating hepatocellular damage) in 24 patients (60%) and splenomegaly in 12.5% of patients.

Lymphadenopathy was found in a single patient. Hepatomegaly was seen in 9 patients (22.5%) and splenomegaly in 5 patients (12.5%). Hepatosplenomegaly was present in 3 patients (7.5%).

Complications and outcome

Two patients expired in the present study which constituted 5% mortality. This could be because the study was done in a tertiary care centre. One was an elderly patient – 83 yrs. old man, and the other was a middle-aged man who was 43 yrs. old. The 83 yrs. old man was being treated for encephalitis, and had no comorbidities. The second person had acute kidney injury and shock. He died on the day immediately after hospital admission. In the study by Ramyasree et al no mortality was reported.¹⁶ Myocarditis, ARDS, pleural effusion, acute kidney syndrome were some of the complications found in 5%, 0.25%, 0.25% 15% respectively in a study by Wang et al.¹⁷

Respiratory complications like pleural effusion, ARDS and pneumonia developed in in one patient each .The lung is one of the main target organs for *Orientia*, leading to pulmonary complications of variable severity as mentioned in various studies.⁵These include varying degrees of bronchitis, interstitial pneumonia, ARDS, pulmonary oedema, hilar adenopathy, focal atelectasis, reticulonodular opacity, bronchial wall thickening and centrilobular nodules.

Myocarditis in scrub typhus is usually subclinical. Two patients developed myocarditis (5%). However this was not associated with increased mortality. In a study on myocarditis in scrub typhus in Korea, the proportion of myocarditis was 14%.¹⁸

Viral infections caused by the varicella zoster virus, the human immunodeficiency virus and coxsackievirus have been reported to cause myocarditis¹⁹.

In comparison, bacterial myocarditis is relatively uncommon¹⁷. *O. tsutsugamushi* is primarily localized in the endothelial cells of the heart, lung, brain, kidney, and skin; and within cardiac muscle cells¹⁸. Subsequently, infection with *O. tsutsugamushi* results in vasculitis in multiple organs, leading to various complications. Among these complications, cardiac manifestations such as myocarditis, pericarditis and infective^{20,21}

ELISA and Weil Felix tests.

Even though molecular diagnostic tests are available now-a-days, it is not feasible in most of the centres. Gold standard tests like Indirect Immunofluorescence assay and Indirect Immunoperoxidase is also equally expensive. The scrub typhus ELISA is a flexible alternative to IFA¹⁴ and has specificities and specificities of > 90% for detecting specific antibodies¹⁵.

All the serum samples were subjected to Weil Felix tests. Nineteen samples gave a titre of more than 1:160 i.e.47.5% of the samples gave a significant titre .Its known that agglutinating antibodies develop to detectable levels only during the second week of illness.65% of patients presented to the hospital before 7 days of fever and most of them were discharged before a second serum sample could be obtained.

Even though it is a test with low sensitivity and specificity, it can still be used in resource poor settings were even ELISA is not available.

CONCLUSION

Scrub typhus is an acute febrile illness that is endemic to our part of the state. This study revealed that 60% of patients were males and most of them belonged to 40 – 59 yrs age group. Eschar was present in 17.5% and bleeding manifestations were present in 10% of cases. Hepatomegaly was present in 37.5% and elevated liver enzymes in 60% cases. It is not a disease of zero mortality. This study has revealed 5% mortality. This

cannot be generalized as this was conducted at a tertiary care centre

The complications in patients who got delayed treatment or who failed to receive treatment resulted in significant morbidity. Complications developed in 40% patients and acute kidney injury was the commonest 37.5%.

Preventive measures during the post monsoon periods can significantly reduce the number of cases. Although the results of this study, reflects the situation in a tertiary care centre, the situation in the primary health care settings could be worse. A course of doxycycline in suspected cases goes a long way in reducing the morbidity and mortality.

ELISA is the main diagnostic tool for laboratory confirmation of cases where molecular methods are not available but Weil Felix test is a feasible alternative in peripheral centres where laboratory infrastructure does not support ELISA.

ACKNOWLEDGEMENT

I am thankful to Smt. Sunitha Kumari lab technician for her assistance in carrying out the lab work.

I am also thankful to the Chairman and members of the State board for medical research for providing the necessary funds for the study.

REFERENCES

1. Hornick RB. Rickettsial Diseases. (Chapter 371). In: Bennett JC, Plum F, editors. Goldman: Cecil Textbook of Medicine. 21st ed. Philadelphia, USA: WB Saunders Company; 2000. p. 1911-2)
2. Chang WH. Current status of tsutsugamushi disease in Korea. *J Korean Med Sci* 1995;10:227-38
3. Mahajan SK. Scrub typhus. *J Assoc Physicians India* 2005;53:954-8
4. Mahajan SK, Kashyap R, Kanga A, Sharma V, Prasher BS, Pal LS. Relevance of Weil-Felix test in 9 to diagnosis of scrub typhus in India. *J Assoc Physicians India* 2006;54:619-21 (to check)
5. Tattersal R N 1945. Tsusugamushi fever in India-Burma border. *Lancet* 2:392- 394
6. Mathai E, Rolain JM, Verghese L, Mathai M, Jasper P, Verghese G et al, Case reports: Scrub typhus during pregnancy in India. *Trans R Soc Trop Med Hyg.*2003;97: 570-2
7. Walker DH, Dumler Js, Marrie T, Rickettsial Diseases. (Part 8, Section 10, Chapter 174) In: Longo DL, Fauci AS, Kasper DL, Jameson JL, Loscalzo J, editors. *Harrisons Principle of Internal Medicine*. 18th ed. Philadelphia: Saunders, Elsevier: 2007. pp. 1295-67.
8. Guang Xu, David H Walker, Daniel Jupiter, Peter C Melby, Christine M Arcari, *PLoS neglected tropical disease*. 2017;11(11):e0006062
9. Kedareshwar P.S., Narvencar, Savio Rodrigues, Ramnoath P. Nevrekar, Lydia Dias, et al Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa.)
10. Chanyasa C, Kaeburong K, Chenthittikul M, Sujirarat. D. Seroprevalence of scrub typhus infection in patients with pyrexia at some nature clinics in 3 western provinces of Thailand. *Asian Pak J Allergy Immunology* 1998; 16: 119-25
11. Kim SJ, Chung IK, Chung IS, Song DH, Park SH, Kim HS, Lee MH. The clinical significance of upper gastrointestinal endoscopy in gastrointestinal vasculitis related to scrub typhus. *Endoscopy*. 2000;32:950–955.
12. Chien RN, Liu NJ, Lin PY, Liaw YF *J Gastroenterol Hepatol*. 1995 Jul-Aug; 10(4):484-7. Acute acalculous cholecystitis and pancreatitis in a patient with concomitant leptospirosis and scrub typhus
13. Wang NC, Ni YH, Peng MY, Chang FY *J Microbiol Immunol Infect*. 2003 Dec; 36(4):285-7.
14. ShiaoCC, Lin SY . Eschar: a clue to scrub typhus *CMAJ*. 2011;183:E1152
15. Outbreak of Scrub typhus in Pondicherry *JAPI* 2010 Jan;58: 24-28.
16. Ogawa M, Hagiwara, T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y et al. Scrub typhus in Japan Epidemiology & clinical features of cases reported in 1998. *Am J Tropical Med Hyg* 2002; 67:162-5)
17. Dash GA, Halle S, Bourgeois AL . Sensitive microplate enzyme-linked immunosorbent assay for detection of antibodies against scrub typhus rickettsia, *Rickettsia tsutsugamushi*. *J Clin Microbiol*. 1979;9: 38 - 48

18. Varghese GM, Abraham OC, Mathai D, Thomas K, Aaron R, Kavitha ML, et al. Scrub typhus among hospitalized patients with febrile illness in South India: Magnitude and clinical predictors. *J Infect.* 2006;52:56-60.
 19. Ramyasree A, Kalawat U, Rani N.B and Chaudhury A. 2015. Seroprevalence of scrub typhus in a tertiary care hospital in Andhra Pradesh. *Ind J. Med. Microbiol.* 33(1): 68-72
 20. Wang CC, Lu SF, Llu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. *Am J. Trop Med Hyg* 2007; 76: 1148-52.
 21. Jung Yeon Chin, Ki-Woon Kang, Kyung Min Moon, Jongwoo Kim, and Yu Jeong Choi. Predictors of acute myocarditis in complicated scrub typhus: an endemic province in the Republic of Korea
 22. Donoiu I, Istratoaie O. Varicella-zoster myocarditis mimicking acute myocardial infarction. *Curr Health Sci J.* 2014;40(1): 78–80.
 23. Haddad F, Berry G, Doyle RL, Martineau P, Leung TK, Racine N. Active bacterial myocarditis: a case report and review of the literature. *J Heart Lung Transplant.* 2007; 26(7):745
 24. Moron CG, Popov VL, Feng HM, Wear D, Walker DH. Identification of the target cells of *Orientia tsutsugamushi* in human cases of scrub typhus. *Mod Pathol.* 2001;14(8):752–9. 1
- How to cite this article: Mathew L, Ragi RG. Scrub typhus - changing trends and varying symptomatology. *International Journal of Research and Review.* 2020; 7(12): 203-209.
