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10.4103/jacm.jacm\_21\_17

# Detection of scrub typhus at a tertiary health centre in Central Kerala

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## Abstract:

**SCOPE:** Scrub typhus is a rickettsial disease caused by *Orientia tsutsugamushi*, transmitted by the bite of *Leptotrombidium* mites. It presents clinically as a non-specific febrile illness and is often overlooked. In India, there are reports of resurgence of scrub typhus. We did a cross-sectional study to detect scrub typhus among patients presenting with fever.

**MATERIALS AND METHODS:** This study was conducted in the Department of Microbiology at a tertiary health centre in Central Kerala from January 2014 to September 2015. Two hundred and eight serum samples collected from patients presenting with fever, and whose serological tests were negative for dengue, leptospirosis, enteric fever and malaria were tested using IgM enzyme-linked immunosorbent assay (ELISA) for *O. tsutsugamushi*.

**RESULTS:** Out of the 208 samples collected, 23 (11%) were positive for scrub typhus by IgM ELISA. The maximum number of cases was found in the age group of 41–60 years (56.5%). All the clinical findings were non-specific. Only one patient had an eschar.

**CONCLUSIONS:** In the present study, we found that scrub typhus is prevalent in the districts of Central Kerala as well. Serological tests are the mainstay of diagnosis of scrub typhus and should be considered in the panel of tests ordered for patients presenting with non-specific febrile illnesses.

## Keywords:

Central Kerala, IgM enzyme-linked immunosorbent assay, scrub typhus

## Introduction

Scrub typhus, also known as ‘tsutsugamushi’ fever, is a rickettsial febrile illness caused by *Orientia tsutsugamushi* which is transmitted by the bite of larvae of *Leptotrombidium* mites (chiggers).<sup>[1]</sup> It is widespread in the so-called ‘tsutsugamushi triangle’ which extends from far Eastern Russia and Northern Japan in the North, to territories around the Solomon sea and Northern Australia in the South and to Pakistan and Afghanistan in the West.<sup>[2]</sup> In India, there are reports of resurgence of scrub typhus from Northern, Northeastern, Western and Southern states,<sup>[3]</sup> including Kerala.

Scrub typhus is underdiagnosed in India due to its non-specific clinical presentation, limited awareness and low index of suspicion among

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clinicians and lack of diagnostic facilities.<sup>[4]</sup> In Kerala, the first cases of scrub typhus were reported from Thiruvananthapuram district in the year 2000.<sup>[5]</sup> Since then, scattered cases have been reported every year from Thiruvananthapuram and Malabar region.<sup>[5]</sup> To the best of our knowledge, there are no published reports of scrub typhus from Central Kerala which includes the districts of Alappuzha, Kottayam and Pathanamthitta. In our hospital, it was expected that a fair proportion of the undiagnosed febrile illnesses would be due to scrub typhus. Hence, we conducted this study to detect scrub typhus in patients presenting with fever.

## Materials and Methods

A cross-sectional study was conducted in the Department of Microbiology at a tertiary

**How to cite this article:** Raghunath P, Paul PJ, Oommen S, Asokan AG. Detection of scrub typhus at a tertiary health centre in Central Kerala. J Acad Clin Microbiol 2018;20:28-32.

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health centre in Central Kerala from January 2014 to September 2015. Ethical clearance was obtained from the Institution Ethics Committee and patient consent was taken before collection of samples.

Serum samples received at the microbiology laboratory for serological workup of acute undifferentiated febrile illnesses from consecutive outpatients and inpatients, which were negative for *Leptospira* IgM enzyme-linked immunosorbent assay (ELISA), Dengue IgM and NS<sub>1</sub> ELISA, enteric fever, hepatitis and malaria, were included in the study. The sample size was calculated to be 200, considering the prevalence of scrub typhus from previous studies.<sup>[6]</sup> The testing was done retrospectively as batched samples using Scrub Typhus Detect™ IgM ELISA, InBios International, Inc. (WA, USA). As per the manufacturer’s specifications, this is a qualitative ELISA for the detection of IgM antibodies in human serum to *O. tsutsugamushi*- derived recombinant antigen. The cut-off value was calculated by taking the mean of the optical density (OD) values of 100 serum samples from healthy donors. This was found to be 0.410 in our locality. OD values above the cut-off were taken as positive. A pre-designed proforma was used for patient data collection, which was entered into Microsoft Excel sheet and analysed using SPSS software version 20.

### Results

A total of 208 patients with undiagnosed fever were included in the study, out of which 23 (11%) were IgM positive for scrub typhus by IgM ELISA. Of the 23 patients, 14 (61%) were male and 9 (39%) were female. Majority of the patients were between 40 and 60 years of age [Figure 1]. Twelve cases were from Pathanamthitta district, six cases from Alappuzha district and three cases from Kottayam district. Out of the remaining two cases, one was a resident of Delhi and one of West Bengal.

The most consistent clinical symptom was fever, of which 47.8% had associated chills. The most significant laboratory findings were raised erythrocyte sedimentation rate (82.6%), elevated transaminases (69.5%) and

thrombocytopenia (60.8%). The clinical parameters and laboratory findings have been enumerated in Table 1.

The seasonal distribution of cases show that in 2014, they were distributed in the post-monsoon season and the cooler months (November, December, January), and in 2015, maximum number of cases were present in the months of June, July and August, the monsoon season [Figure 2].

Out of the 23 cases of scrub typhus, 11 of them had complications, eight patients had to be admitted in the Intensive Care Unit (34.78%). About 26% of the patients had associated acute renal failure [Table 2].

### Discussion

In India, the burden of rickettsiosis is underestimated as there is lack of both community-based studies and availability of specific laboratory tests. Weil–Felix test which is widely used as a screening test for the diagnosis of rickettsial diseases is highly unreliable due to its low sensitivity.<sup>[11]</sup> A high index of suspicion is required to diagnose rickettsiosis, and it should be differentiated from other infections such as meningococemia, brucellosis, malaria, viral illness and typhoid fever as there is an overlap of clinical features. Several studies to find the prevalence of scrub typhus have been published from South India, especially from Tamil Nadu and Pondicherry,<sup>[7,10,12]</sup> but those from Kerala are very few. Few cases were reported from Government Medical College, Thiruvananthapuram in the year 2000.<sup>[5]</sup> Since then, several cases have been reported in clusters from the district.<sup>[5,13]</sup> The first case from the Malabar region was reported in the year 2006, following which several cases are being reported from the districts of Kozhikode, Malappuram, Kannur, Wayanad and Palakkad (unpublished data).<sup>[1]</sup> Recently, few cases of scrub typhus were reported among labourers engaged in grass-cutting activities in Wayanad (unpublished data). To the best of our

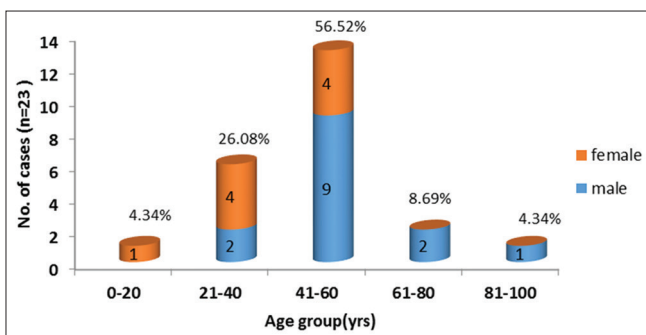


Figure 1: Age-gender distribution among cases of scrub typhus (n = 23)

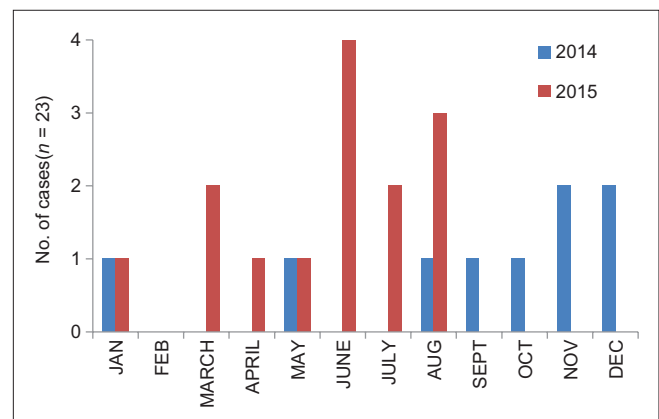


Figure 2: Month-wise distribution of scrub typhus cases in our study

**Table 1: Clinical and laboratory parameters**

Study	Clinical symptoms	Clinical signs	Laboratory investigations
Present study, 2015	Fever - 100% Chills - 47.8% Myalgia - 47.8% Headache - 34.78%	Eschar - 4.3% Hepatomegaly - 13% Lymphadenopathy - 8.6% Generalised rash - 4.3%	Raised ESR - 82.6% Elevated transaminases - 69.5% Thrombocytopenia - 60.86% Hypoalbuminaemia - 47.8% Hyperbilirubinaemia and hyponatraemia - 43.47% Raised serum creatinine - 30.43%
Girija <i>et al.</i> , 2013 <sup>[7]</sup>	Fever - 100% Chills - 66% Myalgia - 95% Cough - 40% Nausea - 28%	Eschar - 4% Hepatomegaly - 3% Lymphadenopathy - 4% Rash - 3%	Elevated transaminases - 20% Thrombocytopenia - 84% Raised serum creatinine - 80%
Inamdar <i>et al.</i> , 2013 <sup>[8]</sup>	Fever - 79.5% Headache - 97% Abdominal pain - 56% Anorexia - 54.5%	Eschar - 75.5% Hepatomegaly - 74% Lymphadenopathy - 52.5% Rash - 45%	
Varghese <i>et al.</i> , 2013 <sup>[9]</sup>	Fever - 100% Myalgia - 32.4% Headache - 42.8% Cough - 37% Altered sensorium - 24.6% Seizures - 6.5%	Eschar - 55% Rash - 1.2%	Elevated transaminases - 72.5% Hyperbilirubinaemia - 26.6% Raised serum creatinine - 12.9%
Vivekanandan <i>et al.</i> , 2010 <sup>[10]</sup>	Fever - 100% Myalgia - 38% Headache - 52% Nausea - 58% Cough - 40%	Eschar - 46% Hepatomegaly - 28% Lymphadenopathy - 80% Rash - 14% Altered sensorium - 20%	Elevated transaminases - 95.9% Thrombocytopenia - 28% Hypoalbuminaemia - 87.5% Hyperbilirubinaemia - 20.5% Raised serum creatinine - 13%

ESR: Erythrocyte sedimentation rate

**Table 2: Complications**

Study	Complications
Present study, 2015	Acute renal failure - 26.08% MODS - 8.7% Meningoencephalitis, myocarditis, bronchopneumonia and acute pancreatitis - 4.34%
Girija <i>et al.</i> , 2013 <sup>[7]</sup>	Acute renal failure - 8%
Inamdar <i>et al.</i> , 2013 <sup>[8]</sup>	ARDS - 11.5% Meningoencephalitis - 8.5% Pneumonia - 5.5% Sepsis - 5%
Varghese <i>et al.</i> , 2013 <sup>[9]</sup>	Acute renal failure - 12.9% MODS - 38.8% Meningoencephalitis - 18.8% Altered sensorium - 24.6% Seizures - 6.5%
Vivekanandan <i>et al.</i> , 2010 <sup>[10]</sup>	Acute renal failure - 12% Meningitis - 14% ARDS - 8% Shock - 4%

MODS: Multiple organ dysfunction syndrome; ARDS: Acute respiratory distress syndrome

knowledge, there is no published report from Central Kerala.

In our study, out of the 208 samples collected, 23 samples (11%) were positive by scrub typhus IgM

ELISA. Prevalence studies have been published from Goa (34%),<sup>[14]</sup> Delhi (48.2%),<sup>[15]</sup> Pondicherry (50 cases over 2 years)<sup>[11]</sup> and Vellore district of Tamil Nadu (47%).<sup>[11]</sup> Data on communicable diseases, given by the Directorate of Health Services (DHS), Kerala, show that the number of reported cases of scrub typhus were 68 in 2013, 433 in 2014 and 1149 in 2015.<sup>[16]</sup> The enormous increase in the number of reported scrub typhus cases over the years can be presumed to be due to increased awareness and suspicion among doctors and subsequent serological confirmation of the disease. The maximum number of cases have been reported from Thiruvananthapuram district in 2013 (49), 2014 (360) and 2015 (947). Reported cases from Central Kerala were, respectively, much fewer.<sup>[16]</sup>

In our study, 61% of the cases of scrub typhus were males. Five of them gave a history of going to paddy fields (21.73%), where two of them were farmers and three of them had an exposure by chance. There was no history of travel. Comparable to our study, a male preponderance for acquiring the infection was observed in studies done by Inamdar *et al.*, KMC Manipal,<sup>[8]</sup> Varghese *et al.*, CMC Vellore<sup>[9]</sup> and Gurung *et al.*<sup>[17]</sup> and the occupation-wise distribution of patients revealed that majority were agriculturists. The low percentage of occupational exposure to scrub vegetation (21.73%) in

our study can be attributed to the increasing urbanisation and decreasing agricultural activities in Kerala when compared to other parts of South India.

The distribution of cases across the year, according to the DHS,<sup>[16]</sup> Kerala state, show a seasonal variation with maximum number of cases in the monsoon and post-monsoon season, reaching a peak during the cooler months of the year, which is comparable to our study [Figure 2]. Similar seasonal distribution has been reported by Mathai *et al.*<sup>[18]</sup> This is because the larvae of *Leptotrombidium* mites require high level of humidity for their survival, and for the same reason, they are found on scrubs and bushes which are commonly seen during the monsoons, rather than on tall trees.<sup>[1]</sup>

A comparison of the clinical parameters, laboratory investigations and complications with previous studies has been given in Tables 1 and 2, respectively.

The diagnostic tests available for scrub typhus include Weil–Felix test, IgM ELISA, indirect immunofluorescence assay (IFA), rapid immunochromatographic tests (ICTs) and polymerase chain reaction (PCR). Weil–Felix test is unreliable due to its low sensitivity.<sup>[11]</sup> IgM ELISA has got high sensitivity and specificity of around 90%,<sup>[11]</sup> and it is helpful for detection of scrub typhus where laboratories are moderately equipped. However, they may give false-positive results due to the presence of rheumatoid factor or other non-specific antibodies in the patients' serum.<sup>[19]</sup> Commercial rapid detection kits such as scrub typhus rapid card test and scrub typhus IgM and IgG rapid immunochromatographic assay (PanBio, Brisbane, Australia) have appeared in the market but are still far from the reach of most of the developing countries due to their high cost. Blacksell *et al.*,<sup>[20]</sup> assessed the diagnostic capacity of a rapid ICT and found that the sensitivity and specificity for the detection of IgM were 96.8 and 93.3%, respectively. IFA, with the high sensitivity and specificity,<sup>[21]</sup> was considered to be the gold standard for serodiagnosis, but the lack of standardisation of endpoints and antigen strains used in the test has resulted in considerable confusion and is no longer considered the same.<sup>[22]</sup> At present, the gold standard test for the diagnosis of scrub typhus is PCR. According to a study conducted in Thailand, the sensitivity and specificity of PCR is 86.5% and 100%, respectively. In addition, this test helps to diagnose patients with inconclusive IFA results. However, it cannot be performed in moderately equipped laboratories due to the high cost involved and trained personnel required.<sup>[23]</sup>

Out of the 23 serologically confirmed cases of scrub typhus in our study, 13 cases (56.52%) were clinically diagnosed as scrub typhus. Analysing the clinical presentation, it was found that eschar, which is the pathognomonic feature,

was documented only in one of these patients (4.3%) and lymphadenopathy in two patients (8.6%). It is suggested by Kim *et al.* that in cases with enlarged or tender lymph nodes, a thorough physical examination of the body area that includes draining lymph nodes, should be considered as a prerequisite for detecting eschars.<sup>[24]</sup> It points to the fact that an eschar would have been missed out in these patients, probably due to lack of thorough physical examination. This finding also emphasises the importance of including scrub typhus in the differential diagnosis of undifferentiated fevers and ordering tests to rule out or confirm the same.

The remaining 10 (43.47%) of the 23 serologically confirmed cases of scrub typhus were not clinically suspected and thus were not investigated further. These cases were missed out by the clinicians, probably due to lack of awareness of the disease in our population. All the 10 cases had presented with fever with chills, four cases with associated myalgia and two cases with headache. Four of these cases were diagnosed as viral fever, five of them as lower respiratory tract and one as urinary tract infection. None of these patients had any complications. The clinical presentation of scrub typhus is very similar to that of viral fevers and there are reported cases of scrub typhus presenting with pneumonia.<sup>[8,13,25]</sup> Most of these patients were treated successfully with azithromycin in accordance to the hospital antibiotic policy.

## Conclusion

The emergence of scrub typhus in Kerala is not known. It is possible that it existed in the past, but went unnoticed as many physicians might have been treating their patients with the commonly used antibiotics such as doxycycline and azithromycin, to which scrub typhus responds, without considering it in their differential diagnoses. Our study highlights that scrub typhus is not only a re-emerging disease of Northern and Southern parts of Kerala but also in the central region which might have been overlooked. Primary care physicians must include scrub typhus as an important differential diagnosis in patients presenting with fever, cough, breathlessness, myalgia, headache, rashes, anorexia, vomiting or abdominal pain and start empirical treatment with doxycycline early in the course of illness. It must also be included in the panel of serological tests ordered in such patients. Further prospective studies with a larger sample size over a span of few years comparing the clinical and laboratory parameters and the outcomes may be done to evaluate the actual burden of the disease in our population. Furthermore, as our state attracts many tourists and as many migrant labourers have been residing here, further studies have to be done to understand epidemiological aspects and strain variability of this re-emerging infection.

## Acknowledgement

We would like to acknowledge the DHS, Kerala state, as the data on communicable diseases was extracted from their official website. We wholeheartedly thank the Department of General Medicine and the Medical Records Department of Pushpagiri Institute of Medical Science and Research Centre, Tiruvalla, for extending their support during the course of our study.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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