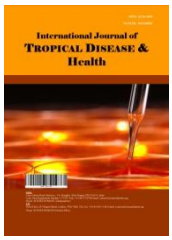

International Journal of TROPICAL DISEASE & Health

43(8): 25-34, 2022; Article no.IJTDH.86130
ISSN: 2278–1005, NLM ID: 101632866

Emergence of Scrub Typhus in Urban Areas: a Report from South India

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Authors' contributions

This work was carried out in collaboration among all authors. Authors RM, RG, VR and PSN were involved in the design, protocol of the study. Authors RM and PSN performed the analysis and wrote the first draft of the manuscript. Authors RS was involved in the literature search and writing the discussion of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2022/v43i830607

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/86130

Original Research Article

Received 12 February 2022
Accepted 26 April 2022
Published 30 April 2022

ABSTRACT

Aims: To study the epidemiology and clinical presentation of Scrub typhus in Southern India.
Study design: Observational study
Place and Duration of Study: Apollo Hospital, Chennai, India, between January 2010 and December 2011.
Methodology: This is an observational study of 182 patients from a tertiary care center between January 2010 and December 2011. Cases of scrub typhus were defined by a positive IgM scrub typhus ELISA, compatible clinical features and negative workup for other pathogens. Epidemiological data and clinical data were collected from the records for the study purpose.
Results: Fever (100%), headache (69.7%) and cough (47.8%) were the predominant presenting symptoms. The majority (85.7%) of cases were during the period from July to December in both the years, corresponding to the monsoon in South India. 62% of cases were from urban areas and 47.3 % of cases required admission to the critical care unit. An eschar was present in 46.7% of cases and 97.3% of the cases improved with therapy. All patients received either doxycycline or azithromycin or a combination of both as therapy. Defervescence was seen within 72 hours in

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98.5% of patients.
Conclusion: Scrub typhus is a re-emerging disease in South India. It should be considered in the differential diagnosis of acute undifferentiated febrile illness even in urban areas in all age groups, especially during the monsoon season. Careful search for an eschar is important. Treatment with doxycycline or azithromycin is effective. The mortality rate is expected to be high if untreated, so we suggest that these antibiotics be part of initial empiric therapy whenever the disease is in the differential diagnosis in all severely ill patients awaiting diagnostic results.

Keywords: Scrub typhus; South India; re-emerging infectious diseases; eschar; doxycycline; azithromycin.

1. INTRODUCTION

Scrub typhus is a potentially lethal, underdiagnosed, re-emerging infectious disease with a higher mortality rate if untreated. There are about a million cases reported annually with one billion people at risk of acquiring the disease [1,2]. It was one of the leading causes of morbidity and mortality during the second world war among the military personnel, following which the disease had been long forgotten only to re-emerge. The widespread use of beta lactam antibiotics which are resistant to *Orientia tsutsugamushi*, antigenic heterogeneity, increased awareness, increased surveillance and better diagnostics are postulated to be reasons for the re-emergence of the disease [3]. Global epidemiology of the disease is expanding beyond the tsutsugamushi triangle (extending from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west) of the Asia Pacific region, with growing evidence of cases being reported in South America, Africa, and France [4,5]. Once considered a rural disease it has now been increasingly recognized in urban areas and these changes are attributed to several factors like urbanization, travel, global warming, resistance to antibiotics and changes in land use [6,7,8].

After being recognized as a typhus like fever in 1917 in India, it was a major cause of fever in borders during the second world war and in the subsequent Indo-Pakistan wars in 1965 and 1990. The decrease in incidence afterwards is attributed to empiric treatment of febrile illnesses, insecticide use and changes in lifestyle. But it is still considered an underdiagnosed disease in India after its resurgence. Cases have been reported throughout most parts of India from Maharashtra to Tamil Nadu, Puducherry, Karnataka, Kerala, Himachal Pradesh, Jammu and Kashmir, Uttaranchal, Rajasthan, West Bengal, Bihar, Meghalaya, and Nagaland [9]. A systematic review of the burden of the disease in India showed that majority of the published cases were from Southern India, 53.3% were agricultural laborers, a vast majority (81.7%) were living in a rural area with proximity to bushes and scrubs, and most cases were reported between the cooler months of the year i.e., August and January [1].

Scrub typhus is caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium belonging to the order Rickettsiales. It is vectored by the larval stages (chiggers) of the Leptotrombidium mites (*L. deliense* and *L. akamushi*). Both mites and rodents act as natural reservoirs though the disease does not manifest in the rodents. The bacterium is maintained in the mite population by transovarial and transstadial transmission. Humans acquire the disease when bitten by the chigger mites and are accidental hosts in this zoonotic disease. Scrub typhus is generally seen in people whose occupational or recreational activities bring them into contact with ecotypes favorable with vector chiggers [3,10]. Following a vector bite which is painless, symptoms develop after an incubation period of 10-12 days which may vary from 6-21 days. The clinical manifestations include fever, myalgia, headache, cough, breathlessness, abdominal pain, lymphadenopathy, maculopapular rash and involvement of different organ systems. The pathognomonic eschar representing the site of a chigger bite is reported between 8-93% of the cases in various studies. The eschar starts as a small papule which increases in size and subsequently undergoes necrosis. It is usually seen in the moist areas of the body including the axilla, groin, inframammary area, neck, waist and the inguinal area [11,12,13]. The disease may further evolve to cause pneumonitis, ARDS (Acute Respiratory Distress Syndrome), myocarditis, acute renal failure, hepatitis, meningoencephalitis, and multiorgan dysfunction leading to hospitalization requiring ventilatory and other organ supports [14].

Indian data shows that scrub typhus contributes to one-fourth of cases of acute undifferentiated febrile illness and the community seroprevalence is 34.2% underscoring the need of widespread knowledge and awareness of the disease [1]. Non-specific symptomatology overlapping with other tropical diseases like dengue, malaria, leptospirosis and enteric fever and the high mortality (as high as 70%) if left untreated, signifies the need for timely diagnosis of this easily treatable disease [14, 15]. This study aims to add more data to understand the disease characteristics better in the Indian population.

2. MATERIALS AND METHODS

The study is an observational study conducted in a 600 bedded tertiary care center located in Chennai, a major metropolis in South India. Patients aged ≥ 18 years diagnosed with scrub typhus between January 2010 and December 2011 (24 months) were included in the study.

The following criteria was used for the diagnosis of scrub typhus: acute febrile illness compatible with scrub typhus with or without an eschar, and with a positive IgM by Scrub Typhus Detect™ IgM ELISA (*InBios* International, Inc.).

2.1 Exclusion Criteria (any one of the below)

- Dengue serology positivity
- Leptospirosis serology positivity (IgM Leptospirosis ELISA)
- Smear positivity for malaria
- Evidence of any bacterial sepsis indicated by a positive blood culture
- Positive H1N1 influenza PCR, urine pneumococcal and legionella antigen
- Diagnosis of enteric fever by blood / stool / bone marrow culture positivity

The data was collected from medical records of the study population in retrospect. The data collected includes clinical history, clinical features, laboratory parameters like complete blood count, liver function test, blood urea, serum creatinine, chest X-ray and the course of the illness till discharge / death and further follow up in the out-patient department. Information regarding possible risk factors for exposure to mite larvae and presence or absence of eschar/ rash was also collected. Descriptive analysis was performed on the data.

3. RESULTS

The number of patients included in our study was 182, out of which 94 were females (51.6%) & 88 were males. The age groups and area of residence of the patients are given in table (1) and (2) respectively. Number of patients from urban area was 113 (62%) and 69 patients (38%) were from rural areas. Among those from urban areas, 105 (93%) lived in an independent house with a garden in their premises. History of recent travel prior to onset of febrile illness was positive only in 8 of the urban patients (4.4%). The month-wise distribution of scrub typhus in the study population is as shown in figure (1). Co-morbidities such as diabetes mellitus, hypertension, bronchial asthma, chronic obstructive pulmonary disease, coronary artery disease and hypothyroidism were observed in 32 (17.5%) patients.

Table 1. Age distribution of the study patients with scrub typhus

Age group	No. of patients (%)
18 - 35 years	36 (19.7%)
36 - 50 years	59 (32.4%)
51 - 65 years	73 (40%)
>65 years	14 (7.7%)

Table 2. Area of residence of the study patients with scrub typhus

State	No. of cases (%)
Tamil Nadu	108 (59%)
Andhra Pradesh	54 (29.6%)
West Bengal	7 (3.8%)
Pondicherry	6 (3.3%)
Andaman and Nicobar Island	3 (1.6%)
Assam	2 (1%)
Kerala	1 (0.5%)
Jharkhand	1 (0.5%)

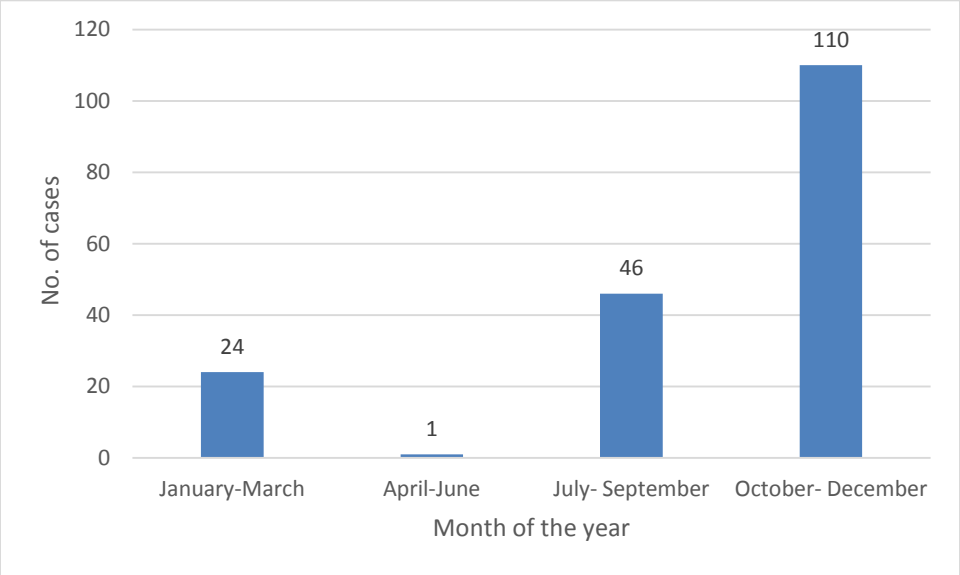

Fig.1. Month wise distribution of scrub typhus patients
Maximum number of cases observed between the months of July and December

Table 3. Frequency of symptoms in the study population

Complaints	% Of patients
Fever	100
Fever > 5 days	32
Fever > 10 days	55
Fever > 15 days	13
Headache	69.7
Cough	47.8
Myalgia	47.8
Shortness of breath	17.5
Abdominal discomfort	14.5
Nausea, vomiting	10.6
Arthralgia	8
Altered sensorium	4.3

Fig. 2. Eschar in a patient with scrub typhus
A black necrotic eschar in the abdominal region of a patient with scrub typhus

Fig. 3. Eschar in a patient with scrub typhus

A black necrotic eschar noted in the neck region of a patient with scrub typhus

Table 4. Frequency of clinical findings in the study population

Clinical finding	% Of patients
Eschar	46.7
Hepatomegaly	25.4
Hepato-splenomegaly	15.2
Splenomegaly	9
Crepitations	21
Hypotension on admission	18
Jaundice	8.6
Lymphadenopathy	7.8
Skin Rash	1.2
Meningeal signs	2.7

Table 5. Laboratory parameters in the study population

Laboratory finding	% Of patients
Hemoglobin < 10 gm%	9.8
WBC count (per cu.mm)	
4000 – 11000	54.4
> 11000	45.6
Platelets < 100,000 cells per cu.mm	11.5
Serum Bilirubin > 2 (mg/dl)	9.9
ALT > 2 times ULN (IU/L)	78
SAP > 2 times ULN (IU/L)	81
Serum Albumin (g/dl)	
< 3.5	33
< 3	27
Serum creatinine > 1.2	9.3

WBC – White blood cell, ALT – Alanine transaminase (IU/L), SAP – Serum alkaline phosphatase, ULN – Upper limit of normal

Table 6. Frequency of complications in the study population

Complication	% Of cases
Pneumonia, ARDS*	17
Septic shock	13.2
Severe hepatitis	9.9
Acute kidney injury	9.3
Acute meningo-encephalitis	2.7

**ARDS – Acute Respiratory Distress Syndrome*

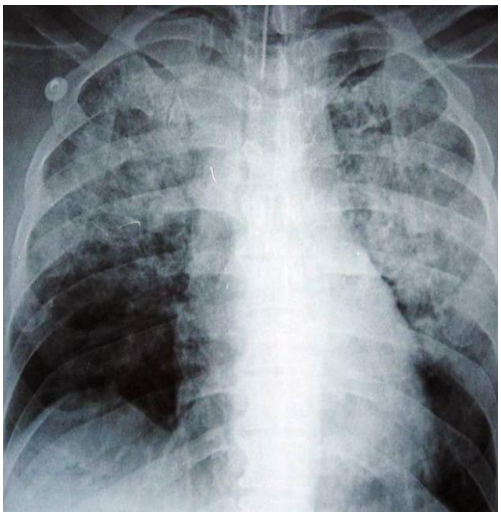

Fig. 4. Chest X-ray of a patient with scrub typhus presenting with ARDS
Chest x ray showing bilateral non-homogenous opacities consistent with ARDS

Fever was seen in all the patients. The duration of fever at the time of presentation varied from a minimum of 2 days to a maximum of 35 days. The other predominant symptoms were as shown in Table (3). The average duration of symptoms prior to the presentation was 10.5 days.

An eschar was seen in 85 patients (46.7%) and all of them had a single eschar. Sites were abdomen (25%), groin (23.4%), chest (18.8%), axilla (15.3%), neck (14%) and face (3.5%). Figures (2) and (3) show eschars seen in abdominal region and neck respectively. Eschars were more common in females (58%) when compared to males (42%). Clinical findings and laboratory findings are as shown in the table (4) and (5) respectively**.**

Almost all patients (95.1%) required hospitalization with a significant proportion (47.3%) requiring admission to critical care unit (CCU). The average duration of hospitalization was 5.2 days for patients admitted in wards and 11.1 days for patients admitted in CCU. The mean APACHE II score on admission in CCU was 19.8. The frequency of complications encountered are described in Table (6). ARDS was seen in 25 patients (13.7%) and 6 patients (3.3%) had pneumonia. Figure (4) shows chest x-ray of one of the patients with ARDS. All these patients required assisted ventilation, 20 (11%) of whom required intubation and mechanical ventilation and the remainder 11 (6%) patients required noninvasive ventilation. Hypotension at the time of admission was present in 33 patients (18%). Inotrope support was required for 20 patients (11%) and the remainder responded to fluids.

Oliguria at the time of presentation was seen in 14 patients (7.7%). Urine albumin was present in 31.6% of the patients. The mean urea value was 42.75 mg/dl and mean serum creatinine was 1.16 mg/dl. The mean GFR was 76.10 ml/min. A diagnosis of acute kidney injury was made in 9.3% of the patients and 6.6% required hemodialysis for a period of 2 to 12 days. None of these patients required long term dialysis. Eight patients (4.3%) had presented with altered sensorium. Cerebrospinal fluid analysis in those showed elevated proteins and raised white blood cell count (WBC) (>10 cells, all lymphocytes) in five patients and it was normal in three cases. Seizure was documented in two patients. Magnetic resonance imaging (MRI) brain done in these patients showed features of meningo-encephalitis in three and was normal in the remainder.

Doxycycline (100 mg oral twice daily) and azithromycin (500 mg intravenous once daily) were used as sole agents for therapy in 62% and 6% respectively whereas 32% received a combination of both. The combination of doxycycline with azithromycin was used predominantly in patients admitted to the CCU. Time for defervescence after initiation of therapy was 48 – 72 hours in 66% and 24 – 48 hours in 32.5%. The average duration of therapy was 12.3 days. Two patients with meningo-encephalitis were treated with chloramphenicol in view of persistence of headache with the combination of doxycycline and azithromycin.

Other antibiotics like beta lactams, glycopeptides were discontinued within 3 – 4 days, once the diagnosis was clear. Almost all patients (97.3%) improved with therapy. Five patients (2.7%) died, and all of them presented to our center with ARDS, and refractory septic shock with duration of symptoms more than two weeks.

4. DISCUSSION

Scrub typhus is a re-emerging zoonotic disease in India, particularly in South India. The exact incidence and prevalence of the disease is difficult to estimate because of the non-specific nature of the illness, low awareness among treating physicians and lack of availability of specific diagnostic tests.

Our study is one of the largest case series of scrub typhus reported from India. Most patients in our study were healthy adults with an average age of 42.6 years and less than one fifth had co-morbid conditions. The median age of presentation in India was 28.1 years in a meta-analysis and 35 years in two different studies from Northern India. The gender distribution is equal in our study population in accordance with other studies from India [1,16,17].

Scrub typhus was thought to be a predominantly rural disease and at least 80% of patients were from rural areas in a meta-analysis [1]. In our study, almost two thirds of the patients were from urban areas and only 4.4% of them had travelled to rural areas. More than one factor may explain this. 93% of our urban cases lived in independent houses with gardens around them, possibly enhancing chigger-human contact. Rapid expansion of urban limits, construction activities and clearing of vegetation followed by appearance of scrub may have expanded the habitat of the chiggers into cities [8]. Notably scrub typhus has also been reported from diverse habitats ranging from seashores to mountain deserts, equatorial rain forests and riverbanks [10]. It is also possible that people from cities were more likely to seek medical attention at a tertiary care center with the availability of diagnostic facilities, whereas the disease may be unrecognized or empirically treated in rural areas.

In our study, 85.7 % of cases were reported during the period from July to December combining the data from both the years, which corresponds to the monsoon and to the wetter months in South India. Meteorological factors such as temperature, humidity and rainfall have been found to be positively associated with the incidence of scrub typhus in several studies [18]. The monsoons in India have the highest rainfall and the humidity also rises during this time. The ambient humidity is found to be an important factor for deciding the distribution and prevalence of the chiggers. Rainfall seems to affect the chigger activity with the rodents during the rainy season. A combination of all these increases the risk of exposure to *Orientia tsusugamushi* during the wetter months of the year as observed in our study [19,20,21].

Scrub typhus can present with nonspecific symptoms. In our study, fever was present in all the patients, followed by headache, cough and myalgia. Other manifestations included shortness of breath, abdominal discomfort, nausea, arthralgia and altered sensorium. More than half of the patients had fever for more than 10 days during presentation. The median duration of fever was observed to be 8 days in a large case series from Uttarakhand in India and 8.8 days in a meta-analysis of Indian studies. The frequency of other symptoms like headache, cough and myalgia were found to be high in our study compared to the metanalysis but were similar compared to studies from northern India [1, 16, 17]. The average duration of symptoms prior to the presentation at our center was 10.7 days and this is reflective of the low index of suspicion of scrub typhus that is prevailing among the doctors.

Apart from being considered pathognomonic, an eschar can also provide a sample for diagnostics like immunohistochemical staining and PCR. Eschar formation was noted in 46.7% of patients in our study. The rates of eschar formation are highly variable from 8-93% in various studies. Eschar was identified in a median of 22% of patients across 94 studies from India. The variability in the incidence of eschar also depends on how carefully the clinical examination was done, geographic location and probably the strain of the bacteria [1,13,14]. Very few patients had regional lymphadenopathy in our study. Eschars are usually found in inconspicuous areas of the body and usually painless; they may be missed and should be carefully looked for. In our study about 57.5% of eschars were found in areas that are not usually examined such as the groin, sub-mammary area, and axilla. In our study only a few patients had generalized lymphadenopathy (7.8%) and skin rash (1.2%). Perhaps because of presentation in

the second week of illness, an early manifestation like maculo-papular skin rash might have been missed. Other clinical findings included hepatomegaly, splenomegaly, lymphadenopathy and jaundice.

Laboratory findings in our study showed a normal WBC count in about half, liver enzyme abnormalities in 80% of cases and thrombocytopenia in 11.5%. Hypo-albuminemia was found in more than half of our cases. It is postulated to be due to increased vascular permeability and an albumin <3 g/dl is known to be associated with severe disease. Most common complication was ARDS (13.7%), followed by septic shock and acute renal failure. Acute meningo-encephalitis was seen in 2.7% of patients. CSF analysis in all these patients showed high protein and lymphocytic pleocytosis. All these findings are consistent with other large studies and meta-analysis documented in the literature. Meningitis was reported to be 16% across 54 studies in India [1,13]. Critical care unit admission was required in almost half of the patients (47%) in our study.

The serological test that we employed for the diagnosis was Scrub Typhus Detect™ IgM ELISA (*InBios* International, Inc.) which detects the presence of IgM antibody to the 56-kDa major outer membrane protein of *O. tsutsugamushi*. This test is reasonably specific and has a quick turnaround time [22]. Though we did not employ Indirect Immunofluorescence antibody (IFA) or Polymerase Chain Reaction (PCR) of eschar tissue or serum to confirm our diagnosis, we carefully selected out cases by ruling out other causes of acute febrile illness in the tropics like enteric fever, leptospirosis, dengue, malaria, and bacterial sepsis.

The time for defervescence with therapy (doxycycline, azithromycin) was within 24-72 hours in 98.5% of cases and the same has been observed in several studies. About one third of our patients received a combination of oral doxycycline and intravenous azithromycin and this was predominantly used in patients admitted to CCU who might not have absorbed oral doxycycline. IV doxycycline was not available in India during this study period. Doxycycline, chloramphenicol, tetracycline, rifampicin and azithromycin are the most studied drugs for scrub typhus. The above antibiotics are found to be equally efficacious according to a meta-analysis of available drug trials. Despite equal efficacy, azithromycin seems more tolerable than doxycycline in view of gastrointestinal adverse effects [23]. There is no clear evidence yet with respect to the drug of choice for the treatment of critically ill patients with scrub typhus. The case fatality rate observed in our study is 2.7% and all of them had ARDS and shock as complications. This rate is less compared to the median of 6% across various studies from India and mortality goes up to 24% in patients with multiorgan failure and 13.6% with CNS involvement [1,24].

5. CONCLUSION

Scrub typhus is a re-emerging disease in South India. It should be considered in the differential diagnosis of acute undifferentiated febrile illness even in urban areas in all age groups, especially during the monsoon season. Careful search for an eschar is important. The clinical presentation is varied, and a significant proportion develops multi-organ involvement requiring intensive care. Treatment with doxycycline or azithromycin is effective. Majority of patients defervesce within three days of initiation of therapy which may be considered as an indirect clinical clue for the disease. The mortality rate is expected to be high if untreated, so we suggest that these antibiotics be part of initial empiric therapy whenever the disease is in the differential diagnosis in all severely ill patients awaiting diagnostic results.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Institutional Ethical Committee approval has been obtained for the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/86130