Original Article

Seroprevalence trends of Scrub typhus among the febrile patients of Northern India: A prospective cross-sectional study

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Abstract

Background: Rickettsial infections remain one of the most neglected and underdiagnosed tropical diseases in the developing countries. Scrub typhus can prove to an important diagnosis in pyrexia of unknown origin (PUO) patients and is transmitted by a species of trombiculid mites ("chiggers"). The disease leads to a plethora of symptoms like fever, rash, headache, nausea, abdominal pain, thrombocytopenia, etc. The current study was aimed to assess the seroprevalence as well as other demographic parameters of scrub typhus among patients diagnosed with PUO in the northern part of India. **Materials and Methods:** This study was undertaken for a period of 3 years from September 2017 to September 2020. Serum samples of suspected cases were tested for IgM Scrub typhus along with other common febrile illnesses like Malaria, typhoid, dengue, leptospirosis, chikengunya, etc. Additional testing for COVID-19 was also planned for samples received after February 2020. **Results:** The overall seroprevalence of Scrub typhus during the 3 year study period was noted to be 18.6% in the PUO patients. Typhoid was noted in 39.5%, malaria in 9.2%, Dengue in 13.5%, leptospirosis in 4.8%, and chikungunya in 5.3% of the patients. No cause was identified in 9.1% of the PUO cases. 3.9% of the samples were positive by RT-PCR for COVID-19. No mortality was noted in the scrub typhus positive cases. **Conclusion:** Scrub typhus is an emerging tropical rickettsial disease in the Indian subcontinent. The present study highlights the importance of screening of PUO cases for this important infection as timely institution of simple empirical treatment can prove to be life saving in such positive cases.

Keywords: Rickettsial, lice, fleas, scrub typhus, trombiculid ,seroprevalence

Introduction

Rickettsial infections have been one of the greatest scourges of mankind, occurring in devastating epidemics during times of war and famine. Rickettsial infections in the past have taken more lives than all the wars combined together. Except Antartica, rickettsial infections are prevalent throughout the world.[1] Geographical distribution of the disease has been historically described to occur within an area of about 13 million km^2 including Afghanistan and Pakistan to the west; Russia to the north; Korea and Japan to the northeast; Indonesia, Papua New Guinea, and northern Australia to the south; and some smaller islands in the western Pacific. This area is famously described as " Tsutsugamushi triangle" (from tsutsuga meaning dangerous and mushi meaning insect or mite).[2,3] This is found only in areas with a suitable climate, plenty of moisture, and scrub vegetation.

Rickettsiae are small, nonflagellate, gram-negative pleomorphic cocco-bacilli who are adapted to obligate intracellular parasitism. They belong to the order Rickettsiales and family Rickettsiaeceae, which currently comprises of three genera – Rickettsia, Orientia, and Ehrlichia.[2] They are transmitted by arthropod vectors and are primary parasites of arthropods like lice, fleas, ticks, and

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mites, in which they are found in the alimentary canal. Being obligate intracellular parasites, these organisms do not grow on cell-free media and need tissue cultures and laboratory animals for their isolation.[2]

The causative agent of Scrub typhus, "Orientia" is an obligate intracellular, small (0.3–0.5 by 0.8–1.5 μm), gram-negative bacterium. It is endowed with a major surface protein (56 kDa) and some minor surface proteins. It does not have a vacuolar membrane; thus, it grows freely in the cytoplasm of infected cells. O. tsutsugamushi has many serotypes which are namely Karp, Gillian, Kato, and Kawazaki. Scrub typhus is transmitted by a species of trombiculid mites ("chiggers"), Leptotrombidium deliense. The disease leads to a variety of common symptoms like fever, rash, headache, nausea, vomiting, and thrombocytopenia. These symptoms are usually shared by a variety of other seasonal diseases such as typhoid, malaria, chikungunya, dengue, and leptospirosis.[4] It is a disease of concern because it can lead to a myriad of serious sequelae like meningoencephalitis, pneumonitis, jaundice, renal failure, myocarditis, and ultimately multiorgan failure as well as death.[5,6]

Due to the lack of proper laboratory confirmation tests, it remains a neglected disease in a developing country like India. Disease has been reported in the last few years from Maharashtra, Tamil Nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam, and West Bengal.[1,2,7-10] Still, the prevalence of disease remains unexplored in Northern India. Hence, the present study was planned to understand the seroprevalence of scrub typhus among patients diagnosed with pyrexia of unknown origin in this northern part of India as well as to assess the various demographic parameters and follow-up in the positive patients.

Materials and Methods

Study Setting and Patient selection: This study was an observational study and undertaken for a period of 3 years from September 2017 to September 2020 in our tertiary care hospital. Institutional ethics committee (IEC) permission was taken before study. All the patients attending the outpatient department or admitted indoors (in any of the departments including Gastroenterology, Neurology, Paediatrics, surgery or Gynaecology wards) suspected of pyrexia of unknown origin (PUO) were included in the study. Exclusion criteria was confirmed cases for other febrile illnesses like malaria, typhoid, dengue, chikungunya, leptospirosis, and unavailability of written informed consent. Febrile patients (both OPD as well as IPD) presenting after February 2020 were also tested for COVID-19 (Coronavirus disease).

Serological testing protocol

Five ml of venous blood was collected in a plain vial without anticoagulant and serum was separated after centrifugation at 3,000 rpm for 5 min. This serum was used for further testing. Detection of IgM antibodies to Scrub Typhus was performed in all the cases of pyrexia of unknown origin (PUO) by *InBios* ELISA kit (InBios International, Inc., Seattle, Washington, USA) for confirmation of scrub typhus. Test was carried out as per manufacturer's instructions and optical density (OD) was read at 450 nm. Result interpretation was as follows: Values <0.2 OD units = negative, 0.25–0.5 OD units = equivocal, and 0.5 OD units = positive. Equivocal samples were subjected to repeat testing after 1 week. For the assessment of specificity of the above ELISA kit, 10 positive samples each of Typhoid, Dengue, and Leptospirosis were tested as controls.

Testing for other febrile Infections:

Samples were tested for other infections in the following manner:

a. Malaria by SD Bioline rapid test kit for P. falciparum and P. vivax
b. Typhoid by Widal test for TO, TH, AH, BH titres (*Tulip diagnostics*)
c. Dengue by *Panbio* ELISA kit
d. Chikungunya by SD and *NIV ELISA* kit
e. Leptospirosis by DRG kit for IgM detection
f. COVID -19 testing by RT-PCR *DIAGSure*™ Multiplex, *TaqMan* based kit manufactured by *GCC BIOTECH* in oropharyngeal and deep nasal swabs.

Patient follow-up:

Information on patient profile, underlying diseases, and other comorbidities during the episode, type of infection, use of invasive procedures, duration of hospital stay, and the outcomes was kept in computer database and analyzed. Follow-up visits of the patient were recorded from the out-patient department for the treatment outcomes.

Statistical analysis

Data was analyzed using the SPSS (Statistical Package for Social Sciences) software for descriptive statistics, and the results were expressed in proportions, mean, and standard deviation. Categorical data were described using numbers and percentages. Statistical significance was calculated by *P* value.

Results

A total of 1,067 patients diagnosed with PUO were enrolled during the study period of 3 years. The median age group of the patients was 38 ± 5 years and the range being 8–62 years. Males comprised of the majority of cases 732 (68.2%) as compared to females 335 (31.8%). Children in the age group of 8–15 years contributed to 6.6% (70) of the total PUO cases.

The seroprevalence of Scrub typhus varied from 24.4% in 2018, 18.9% in 2019 to 12.7% in 2020. Hence, the overall seroprevalence during the 3 year study period was noted to be 18.6% (198) in the PUO patients, while testing for other febrile illnesses revealed Typhoid/Enteric fever in 39.5%, malaria in 9.2%, Dengue in 13.5%, leptospirosis in 4.8%, and chikungunya in 5.3% of the patients. [Figure 1] No cause was identified in 9.1% of the PUO cases. All the 30 control samples tested for checking

the specificity of Scrub typhus ELISA kit tested negative for Scrub typhus. Looking gender wise for the positivity of scrub typhus, males accounted for 29.6% (217/732) out of the total male population, whereas females for 24.7% (83/335) out of the total female population. Age group of 30–60 years contributed for the majority of positive cases 61% (183/300) among various age groups. [Figure 2] Seasonality of the positivity of Scrub typhus positive cases were also assessed revealing maximum positive cases (41%) in the rainy season of each year starting from mid-June to September.

During this COVID times of year 2020, we also analyzed the samples received after February 2020 for the COVID-19 infection in febrile patients. Out of 176 samples received in this defined time period, only sevem samples, that is, 3.9% were positive by RT-PCR for COVID-19. An interesting feature was also identified in two PUO cases, where coinfection with COVID-19 was seen along with Scrub typhus.

On studying the clinical features and symptoms of the patients on presentation to our clinical setting, fever was noted to be the most common presenting feature (100%), followed by chills and rigor (89%), rash (56%), and abdominal pain (42%). Other symptoms included cough, headache, pallor, lymphadenopathy, hepatosplenomegaly, pedal oedema, oliguria, etc. Eschar was noticed or reported by patients only in 8.9% of the positive cases [Figure 3]. Rash, headache, and pallor were the three symptoms found to be statistically significant in scrub typhus positive patients as compared to patients positive for other febrile illnesses (P-value < 0.001). Detailed comparison of various clinical features in Scrub typhus positive and negative patients is enlisted in Table 1. Convulsions, epistaxis, gum bleeding, and cyanosis were not noticed or found in any of the cases. Hepatic impairment and oliguria were seen in almost 19% of the cases. Further workup of the biochemical investigations of the positive patients revealed increased levels of liver transaminases as well as CRP (C-reactive protein) in Scrub typhus positive patients (55.7%) as compared to other febrile illnesses. Mortality was not seen in any of the positive scrub typhus patients. However, a single patient of coinfection with scrub typhus as well as COVID-19 developed respiratory complications on 4th day of hospitalization in ICU went on mechanical ventilation and was on vasopressive drugs till 14th day. The patient was monitored and started with COVID-19 medications in the form of immunomodulators and antivirals along with Doxycycline and was subsequently discharged in good general health on 34th day of hospital admission.

Discussion

Scrub typhus contributes to a majority of PUO cases in a developing country like ours and can prove to be a significant threat in clinical settings in case of late or misdiagnosis. The overlapping symptoms with other common febrile diseases and lack of proper specific laboratory tests makes this disease even more serious and difficult to treat. Various rapid slide agglutination tests have also been evaluated for early diagnosis of this infective condition but they lack proper specificity and sensitivity. ELISA for IgM antibodies can prove to be highly

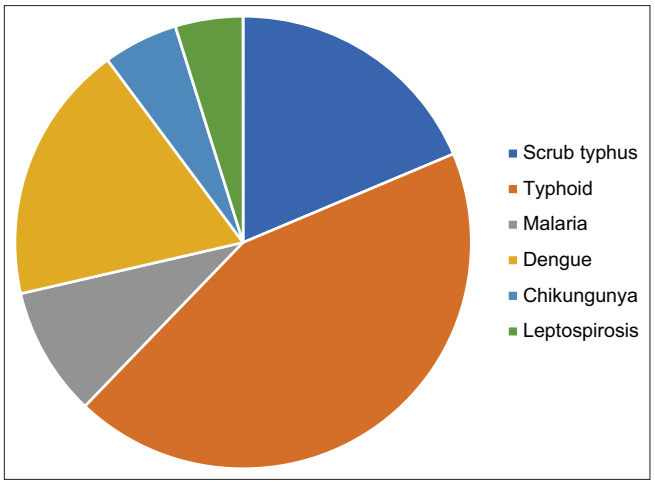

Figure 1: Comparative frequencies of Seroprevalence of Scrub typhus and other febrile illnesses

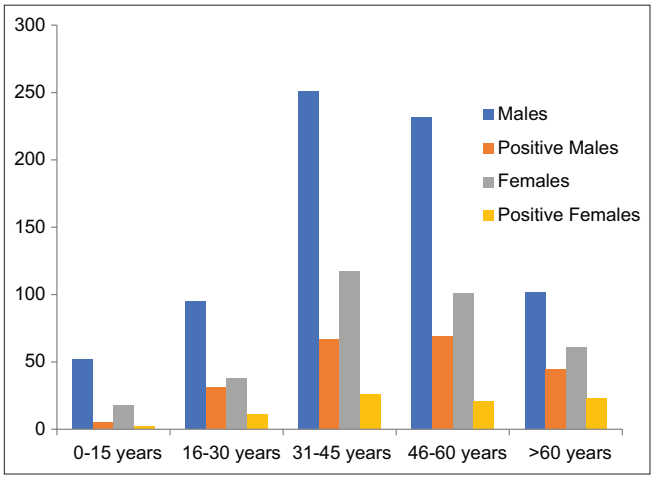

Figure 2: Age and gender wise distribution of total and Scrub typhus positive patients

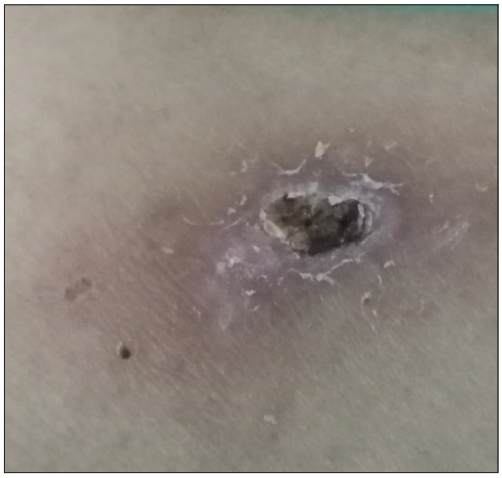

Figure 3: A typical eschar of Scrub typhus with black central lesion and an erythematous boundary

Table 1: Comparison of Symptoms & Clinical features in Scrub typhus and other febrile illness positive cases

Symptoms/Clinical presentation	Scrub typhus positive (*n*=198,18.6%)	Other Febrile illness positive (*n*=869, 81.4%)	*P*
Fever	198 (100)	847 (97.5)	
Chills/Rigor	177 (89.2)	683 (78.6)	
Rash	112 (56.4)	54 (6.2)	<0.001
Abdominal pain	84 (42.6)	445 (51.2)	
Cough	66 (33.4)	259 (29.8)	
Headache	97 (48.9)	36 (4.1)	<0.001
Pallor	101 (51.2)	62 (7.1)	<0.001
Vomitting	82 (41.5)	241 (27.8)	
Cough	42 (21.3)	298 (34.3)	
Hepatosplenomegaly	65 (33.1)	153 (17.6)	
Convulsions	0	0	
Icterus	35 (17.6)	97 (11.2)	
Eschar	18 (8.9)	0	
Myalgia	68 (34.2)	185 (21.3)	
Lymphadenopathy	46 (23.4)	157 (18.1)	
Epistaxis	0	42 (4.8)	
Gum bleeding	0	28 (3.2)	
Cyanosis	0	0	
Pedal oedema	70 (35.6)	184 (21.2)	
Oliguria	38 (19.1)	106 (12.2)	
Increased CRP levels	104 (52.4)	107 (12.3)	*P*<0.001
Deranged Liver transaminases	117 (59.0)	94 (10.8)	*P*<0.001

specific, economical, and cost-effective in diagnosing and managing the patient.[10]

The seroprevalence of scrub typhus in the current study was noted to be around 18.6% during a time span of 3 years varying from 24.4% in 2018, 18.9% in 2019, to 12.7% in 2020. In a similar study by Rizvi *et al.*, from northern India diagnosed 25.5% of the patients with scrub typhus fever by IgM ELISA.[11] Another study from Southern India reported 14.2% prevalence rates of Scrub typhus from rural settings.[12] These findings were very much similar to our study. Our study reported maximum clustering of cases during the rainy season starting from June to September, accounting for 41% of the total cases. Various studies in the past have also clarified this point of predominance of cases in the rainy season as compared to the summer months due to the increased disease transmission by mites during these rainy months.[13,14] The current study reported age group of 30–60 years to be maximally affected by this disease. This is very much comparable to a similar study done in Rajasthan, India by Bithu *et al.*, where majority of patients belonged to this older age group.[13]

Some recent studies during the last 2 years have also tried to assess the endemicity of Scrub typhus in our sub-continent. One study by Devamai *et al.*,[15] from south India reported the prevalence as 20.4% and Kamble *et al.*,[16] from Gorakhpur, India as 19.7%. Scrub typhus has also been studied as a cause of acute encephalitis syndrome (AES) in a study from North India by Jain *et al.*,[17] where scrub typhus alone accounted for 25% of the total AES cases.

Further we deepened our analysis in the current study by assessing the prevalence rates of other febrile illnesses. Typhoid/Enteric fever was identified in 39.5% PUO cases, malaria in 9.2%, Dengue in 13.5%, leptospirosis in 4.8%, and chikungunya in 5.3% of the patients. A similar study on PUO cases revealed comparable prevalence rates of leptospirosis and dengue in these group of patients.[15,16] All the samples of Widal, Dengue, and leptospirosis positive patients tested Scrub typhus negative by The *InBios* IgM ELISA kit. Hence, proving the specificity of the above kit for diagnosis of Scrub typhus. The current study also assessed the presence of COVID-19 in PUO patients as COVID-19 has emerged as a global pandemic affecting millions of people worldwide and is proving to be a greater danger than MERS and SARS Coronaviruses. Most common symptom cluster of COVID-19 encompasses: Respiratory: cough, sputum, shortness of breath, fever; Musculoskeletal: myalgia, joint pain, headache, fatigue; Enteric: abdominal pain, vomiting, diarrhea; Mucocutaneous (less commonly).[17] Here, we studied the positivity for COVID-19 as 3.9% in our PUO cases.

The present study revealed fever with chills and rigor, rash and abdominal pain as the predominant symptoms in Scrub typhus positive patients. Significant association (*P*-value < 0.001) of rash, headache, and pallor was noted among patients infected with Scrub typhus. Studies done by Mittal *et al.*[10] and Rathi *et al.*[7] also noticed rash in almost 49% of the scrub typhus positive patients. Eschar was present in 8.9% of our cases. A very similar rate of presence of eschar 9.5% was noticed in a study by Mahajan *et al.*[2] and 7.2% by Sonthayanon *et al.*[18] However, some studies have also reported a higher incidence rates 55% of presence of eschar in scrub typhus positive patients.[17] Presence of eschar is a highly variable phenomenon and may go unnoticed by both the patient as well as the clinician. Convulsions, epistaxis, gum bleeding, and cyanosis were not identified in any of our Scrub typhus positive patients. Previous literature search also reported very few or low incidence

rates of these clinical features.[17,18] Further workup planned in the form of biochemical investigations revealed higher CRP and liver transaminase values (55.7%) in scrub typhus cases. This is very much in concordance to the finding of Varghese *et al.*[17] who also reported similar rates of raised biochemical markers in these group of positive patients. Raised CRP levels along with other markers was also noticed in a study by Rathi *et al.* from India.[7,19]

No mortality was reported because of the infection by Scrub typhus as the simple empirical treatment by Doxycycline proves to be highly efficacious in positive cases. Previous studies also reported no significant mortality due to scrub typhus infection alone in case of timely diagnosis and institution of treatment.[24-26]

Conclusion

The exact data on the seroprevalence of Scrub typhus in the developing countries is very scanty and the disease still remains underreported in these regions. The current study highlights the importance of primary care physicians in screening the PUO patients presenting to the peripheral centres and guiding them about the correct diagnosis as well as management of this emerging rickettsial infection. Timely institution of empirical treatment in these positive cases will avoid long-term complications and sequelae in the Scrub typhus patients. IgM ELISA can hence prove to be a very specific and economical diagnostic aid for the laboratories and can guide the clinicians toward proper and accurate management of this emerging treatable infection. Future studies should focus more on the vector host relationships in scrub typhus patients and also determine the longevity of IgM antibodies following infection for more meaningful interpretation of seroprevalence data.

Author's contribution

S.S., C.S. performed literature search, data analysis, and first draft of the manuscript and figures. SSP and UG contributed with the final draft of the manuscript and editing.

Ethical considerations

Informed consent was obtained from all the patients and their legal guardians (in case of minors) regarding the publication of images and clinical information in the journal. They were informed of the confidentiality of tha data, however, the anonymity cannot be guaranteed.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

Abbreviations

PUO – pyrexia of unknown origin, COVID – coronavirus disease, PCR-Polymerase chain reaction.

Key Messages

The current study highlights the importance of primary care physicians in screening the PUO patients presenting to the peripheral centers and guiding them about the correct diagnosis as well as management of this emerging rickettsial infection. Timely institution of simple yet effective therapy of Doxycycline or azithromycin for 5 days in these positive cases will avoid long-term complications and sequelae in the Scrub typhus patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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