# **Original Research Article**

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# Clinical profile and seroepidemiology of scrub typhus and its concurrent infections associated with other tropical fevers: a two-year study from a tertiary care centre in North India

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#### **ABSTRACT**

**Background:** The study showed epidemiological aspects, clinical profile and laboratory features of patients presenting with scrub typhus alone and scrub typhus along with concurrent infections namely typhoid, malaria, leptospira, chikungunya and dengue.

**Methods:** A total of 383 suspected cases of Scrub typhus were tested by IgM ELISA from January 2017 to October 2018. Appropriates tests were performed to determine the coinfections of scrub typhus with dengue, chikungunya, malaria, leptospirosis and typhoid fever.

**Results:** Of the 383 samples received, 68 were positive for scrub typhus. Commonest clinical manifestations were fever, shortness of breath, myalgia, headache and jaundice. Maximum number of co infection cases were observed along with dengue.

**Conclusions:** With the rapidly changing epidemiology of scrub typhus, it is very important to become familiar with its clinical presentation when presenting alone and as a concurrent infection with other acute febrile infections.

Keywords: Zoonotic disease, Scrub typhus, Orientia tsutsugamushi, Co-infection

# **INTRODUCTION**

Scrub typhus is a re-emerging acute infectious disease caused by Orientia tsutsugamushi (formerly classified in genus Rickettsia) widely reported from the 'Tsutsugamushi triangle', which includes broad areas of South and South-eastern Asia, the Asian Pacific Rim and northern Australia. It is an acute infectious disease of varying severity, transmitted by mites belonging to the Trombiculidae family. Clinical diagnosis of scrub typhus is very difficult in the early stages of the illness due to many factors like low index of suspicion, nonspecific signs and symptoms and lack of diagnostic facilities.<sup>1,2</sup> Scrub typhus has recently re-emerged as an important cause of acute febrile illness (AFI) in many parts of India,

especially during the monsoon and post monsoon seasons. Out of the 29 states in India, twenty three have reported the presence of scrub typhus.<sup>2</sup> With the changing epidemiology of scrub typhus and the constraints in the diagnosis, it is very important to get familiar with the clinical and laboratory parameters of Scrub typhus, so as to differentiate it from other aetiologies of AFI.<sup>3-5</sup>

Recently cases of scrub typhus co infection with other tropical diseases have been reported. The co-infections commonly reported include dengue, chikungunya, malaria, leptospirosis, and typhoid fever. The reason behind the occurrence of these co infections can be attributed to the fact that most of these infections occur in the monsoon season which coincides with that of scrub

typhus. All these vector borne and water borne tropical infections are commonly seen in the Indian subcontinent and have almost similar clinical manifestations. They also exhibit a similar seasonal presentation. Co-infections of scrub typhus with malaria, leptospirosis and typhoid fever have been frequently reported from the endemic areas, which often leads to either under diagnosis or over diagnosis and mismanagement resulting in either under treatment or over treatment.<sup>5,6</sup> So it is very important that the clinicians should be knowledgeable about the occurrence of dual infections so as to make an accurate diagnosis in order to provide a suitable treatment. Hence this co-relational study was planned in order to determine the clinical and epidemiological profile of patients with scrub typhus and to estimate the prevalence of co infections of scrub typhus along with malaria, leptospirosis, typhoid fever, dengue and chikungunya.

#### **METHODS**

This prospective observational study was conducted in a tertiary care centre in North India from January 2017 to October 2018. Consecutive samples of a total of 383 clinically suspected cases of scrub typhus who presented to the outpatient/inpatient departments were included in the study. Patients less than 2 years of age and those having a history of intake of antibiotics or anti-malarial drugs were excluded from the study. A detailed history and findings on clinical examination were noted. The patients included in the study were subjected to a battery of investigations like complete blood count, peripheral smear, urine analysis, renal function tests and liver function tests.

Diagnosis of scrub typhus was done using IgM ELISA (In BiOS International, Inc. Seattle USA) following the manufacturer's instructions. The samples having an optical density of >0.5 were considered positive. In order to detect the presence of co-infections among the Scrub typhus positive cases, tests for detection of malaria, dengue, leptospirosis, chikungunya, and enteric fever were performed. Peripheral smear and rapid antigen test using rapid kits (by YBIO, India) were used for the diagnosis of Malaria. For Dengue, NS1 antigen and/or specific IgM antibodies detection was done by MAC ELISA kits supplied by National Institute of Virology (NIV), Pune, India. For diagnosis of Chikungunya IgM ELISA (NIV, India) and Leptospira IgM ELISA (Panbio Ptv., Ltd., Oueensland, Australia) were used and tested as per the manufacturer's instructions. Enteric fever was diagnosed by detection of IgM and IgG antibodies using commercially available rapid immunochromatographic test (Is-It by Med Source Ozone pvt. Ltd, India).

The data was recorded in MS excel spreadsheets and the statistical analysis was performed using the same software. Ethical clearance was taken from Ethics Committee of our Institute (Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, INDIA), as per Ethical certificate no. 1069. Written informed consent

was obtained from each study subject or guardian of the wards and confidentiality of the participant's test results was ensured throughout the research.

#### **RESULTS**

A total of 383 patients with clinical suspicion of scrub typhus who presented to the hospital were studied over a period of two years. Out of these 383 clinically suspected patients, 68 were positive for scrub typhus. Age and sex wise distribution of the scrub typhus positive cases has been demonstrated in Table 1. Most of the cases presented during the month of September 2018. They were residents of Delhi and adjoining states like Haryana and Uttar Pradesh. The average duration of fever before presenting to the hospital was around 6 days.

Table 1: Demographic details of the scrub typhus positive patients (n=68).

Age	2017		2018		Total
Less	Males	Females	Males	Females	
than					
14	2	1	19	13	35
years					
More than	Males	Females	Males	Females	
14 years	5	3	13	12	33

Table 2: Clinical symptoms and signs in serologically confirmed scrub typhus patients (n=68).

Variables	No. of patients	Percentage
Symptoms		
High grade fever with chills and rigor	68	100
Shortness of breath	23	33.8
Myalgia	19	27.9
Headache	18	26.4
Rash	18	26.4
Jaundice	9	13.2
GI symptoms	9	13.2
Behavioral change	8	11.8
Seizures	8	11.8
Sore throat	2	2.9
Signs		
Pallor	46	67.7
Hepatomegaly	29	42.6
Splenomegaly	20	29.4
Lymphadenopathy	8	11.8
Eschar	8	11.8

The commonest presenting symptom was high grade fever associated with or without chills and rigors in 100% (n=68) of the patients, followed by shortness of breath (34%), myalgia (28%), arthralgia (27%) and headache

(26%) along with jaundice (13.2%), abdominal pain (16.9%), rash (26.4%) and behavioural changes (11.8%). The details of clinical spectrum are shown in Table 2. Laboratory parameters in serologically confirmed scrub typhus patients has been depicted in Table 3. Out of the 68 positive cases for scrub typhus, 23 (34%) developed pulmonary complications with breathlessness and ARDS requiring endotracheal intubation and mechanical ventilation. Six patients presented with CNS complications like altered sensorium, seizures, headache and neck rigidity. Patients were exhaustively worked up and no other cause of encephalitis/meningitis could be established. One patient developed acute renal failure requiring dialysis.

All of the patients were successfully treated and there was no mortality. The cases of coinfections detected on testing the samples of scrub positive cases (n=68) for malaria, dengue, chikungunya, enteric fever and leptospirosis have been shown in Table 4.

Table 3: Laboratory parameters in serologically confirmed Scrub typhus patients (n=68).

Laboratory parameter	No. of patients (%)
SGOT/SGPT (≥2 times normal)	37 (54.4)
Thrombocytopenia (<1X10 <sup>9</sup> /µl)	48 (70.5)
Hyperbilirubinemia (>2.5 mg/dl)	28 (41.2)
Anaemia (<11 g/dl)	51 (75)
Leukopenia (<4,000/μl)	2 (2.9)

<sup>\*</sup>SGOT/SGPT: serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase.

Table 4. Patients presenting with coinfections with Scrub typhus.

Co infection	No. of patients
Malaria	4
Enteric fever (rapid test)	6
Dengue (IgM antibodies)	5
Dengue (NS1 antigen)	3
Leptospira	1
Chickungunya	0

<sup>\*\*</sup> One patient had coinfection of all three infections i.e. scrub typhus, Dengue and Enteric fever all three infections.

# **DISCUSSION**

Scrub typhus is an infective zoonotic disease, caused by *O. tsutsugamushi*. In humans, it is transmitted by the bite of trombiculid mites which inhabit scrub vegetations. In India, this infection was widely reported during the World War II from Assam and West Bengal borders. Ever since then, scrub typhus has been reported from all parts of the country, mainly from South India and the Himalayan region. Recently outbreaks of the disease have been

reported from many areas of North and Central India.<sup>1-8</sup> In the present study, we observed a post monsoon surge of Rickettsial cases, as has been reported in earlier literature from India.<sup>8-10</sup> Though the secondary scrub vegetation grows in post monsoon period, in the present study, a definite exposure to scrub vegetation was seen in only 10% cases. This indicates that further studies are required to determine the effect of environment on the propagation and life cycle of trombiculid mite (vector of scrub typhus).

The patients in this study presented with diverse clinical symptoms and signs. The commonest presenting symptoms being high grade fever with chills, shortness of breath and myalgia, headache and jaundice which are in accordance to the earlier studies. 1,10-14 The percentage of patients presenting with altered sensorium and seizures was 11.6% and the pathognomonic eschar was seen in 11.8% of the patients, which is similar to that in the previous studies. 1,10,12-14

Thirty-seven patients had elevation of serum transaminases, without evidence of any multiorgan dysfunction. Similar findings have been reported in other Thrombocytopenia, studies also. anaemia. hyperbilirubinemia and leucocytosis were the other common laboratory findings noted in the study. However, these findings may require validation in a larger number of samples. The case fatality rate in our study was low as compared to that of other studies. This may be due to the increased awareness about the disease and a high degree of clinical suspicion.<sup>1,10</sup>

Several case reports of co-infections of scrub typhus with malaria, typhoid fever and dengue have recently been published.<sup>15</sup> However, this study demonstrates the various co infection cases associated with scrub typhus (Table 4). Though the gold standard tests for the diagnosis are immunofluorescence antibody test or PCR; but ELISA is a simple and commonly performed serological test for the diagnosis of scrub typhus. In the present study, ELISA for IgM antibodies against O. tsutsugamushi was used for the diagnosis. The inability to perform PCR or immunofluorescence was a limitation of the study, as it is performed only in specialised laboratories. Another limitation is of overlapping of clinical manifestations among these tropical infections. Our patients who were detected positive for IgM antibodies against scrub typhus by ELISA evoked a very high degree of clinical suspicion and responded well to anti rickettsial treatment. High number of co infections reported in the study could be due to the presence of similar epidemiogical factors responsible for scrub typhus and other tropical infections. However, the possibility of antigenic cross-reactivity should also be kept in mind. Three cases in this study who showed co-infection of scrub typhus and Malaria, presented with severe manifestations. These patients were positive for malarial parasite by peripheral smear (gold standard) and were given both anti-malarial and anti rickettsial treatment. They showed complete recovery.

<sup>#</sup> One patient was positive Dengue IgM Antibodies and Dengue NS1 Antigen positive

This indicates clearly that these three patients were cases of co infection, thus ruling out the possibility of any cross reactivity. Hence, it is very important to rule out the possibility of the occurrence of concurrent infections especially in tropical countries.

# **CONCLUSION**

With the changing epidemiology of scrub typhus, it is now considered to be one of the commonest causes of acute febrile illnesses in India. A high index of suspicion and an early diagnosis is warranted for appropriate patient management and prevention of complications. During the post monsoon season due to the upsurge of various types of vector breeding, the possibility of co-infections should always be kept in mind. The findings of this study will help in increasing the awareness as regards the disease presentation, clinical features and laboratory findings of scrub typhus and other co-infections as causes of acute febrile illnesses in the tropical countries. This knowledge will further help to reduce the mortality due to these infectious diseases in our clinical settings.

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