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Epidemiology and Clinical Features of Scrub Typhus Patients in North India: A Retrospective Case Series

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Abstract

Rickettsiosis, also called Rickettsial infection, is a zoonosis characterized by acute febrile illness. The causative organism is an obligate intracellular gram negative bacterium belonging to the genera *Rickettsia,* Orientia, Ehrlichia, Neorickettsia, or Anaplasma. Scrub typhus is the most common rickettsiosis prevalent in India [1].

Keywords: Rickettsiosis; Rickettsial Infection; Scrub Typhus; Eschar

Abbreviations

HIV: Human Immunodeficiency Virus; WFT: Weil-Felix Test; IIF: Indirect Immunofluorescence; ELISA: Enzyme Linked Immunosorbent Assay; ESRI: Environmental System Research Institute; ICMR: Indian Council of Medical Research; NIMR: National Institute of Malaria Research; ICU: Intensive Care Unit; TLC: Total Leukocyte Count; DLC: Differential Leukocyte Count; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; GGT: Gamma Glutamyl Transferase; ALP: Alkaline Phosphatase

Introduction

Scrub typhus, also known as Tsutsugamushi disease (derived from two Japanese words 'tsutsuga' meaning dangerous and 'mushi' meaning insect or mite), is a vector borne disease endemic in the 'tsutsugamushi triangle' which encompasses South Asia, South-East Asia, East Asia, Pacific Islands and Northern Australia [2-5]. It is also reported from Africa, the Middle East region, and South America and may be considered ubiquitous [3,6].The disease is so called due to the dense secondary vegetation dominated by stunted trees or bushes (known as scrub), that is formed after clearance of the primary forest, which harbors the vector [2,7].

The infection is caused by *Orientia tsutsutgamushi* (formerly called *Rickettsia tsutsugamushi*), which is transmitted to humans via the infected chiggers or larvae of trombiculid mites (*Leptotrombidium deliense* and other species) [2-5]. The primary reservoir for *Orientia tsutsugamushi* are mites and humans are accidental hosts [5]. Recently, newer vectors have also been reported in the literature. These include the mites *Schoengastiella ligula* (India) and *Euschoengastia koreaensis* (South Korea) [3]. Locales (riverbanks, forest clearings, and tall grass) with high relative humidity (60%-85%) and high temperatures as seen in tropical climates, less sunlight, dense secondary vegetation, and more rainfall (called Typhus Islands) provide optimal conditions for the infected mites to thrive [2,3]. Socioeconomic status and occupation are the other risk factors associated with this disease [5]. Farmers, tea garden workers, field workers, and people engaged in outdoor and leisure activities (trekking, camping etc.) in such areas are susceptible to this infection [5,8].

Annually, one million people are affected with scrub typhus all over the world and around one billion are at an increased risk of developing the disease [5,7]. The mortality rate is reported to be 7%-30% [7]. The disease is underestimated due to lack of awareness coupled with inadequate laboratory techniques and diagnostic expertise in most geographical areas [1,4,5,7]. Scrub typhus presents as an acute febrile illness with non-specific signs and symptoms [7]. The clinical manifestations observed in affected individuals include non-specific flu-like symptoms, fever, rash, myalgia, cough, generalized lymphadenopathy, nausea, vomiting, and abdominal pain [5,7]. A pathognomonic eschar develops as a papule at the site of chigger bite, which later becomes necrotic with a black crust (resembling a skin burn from a cigarette), occurring prior to the onset of fever and other symptoms. However, eschars are more commonly observed among Caucasians and East Asians than South-East Asians [5,7]. Scrub typhus infection should be differentiated from malaria, dengue fever, leptospirosis, viral hemorrhagic fever, meningococcal disease, infectious mononucleosis, and Human Immunodeficiency Virus (HIV) [5,6,7,9].

The clinical diagnosis is generally based on the patient's history and presenting symptoms. However, the non-specific symptoms and signs observed in scrub typhus make the diagnosis difficult. Therefore, more specific laboratory investigations such as serology remain the mainstay for diagnosis [7]. Quick and easy diagnosis of the etiologic agent in rickettsiosis including scrub typhus is possible by detecting a significant rise in the antibody titer during the course of infection and convalescence. Several serological tests such as Weil-Felix Test (WFT), Indirect Immunofluorescence (IIF), and Enzyme Linked Immunosorbent Assay (ELISA) help in diagnosis [2].

Scrub typhus is a widespread zoonosis in Asia. In the past, many cases of this illness have been reported from non-endemic areas and plain terrains, which pose a diagnostic challenge [7]. Early diagnosis and timely treatment can prevent complications and morbidity associated with this disease. Therefore, the aim of this study was to describe the epidemiological and clinical features of scrub typhus and rickettsial infection in patients admitted to a tertiary care hospital in New Delhi.

Case Series

A retrospective study was conducted at Max Super Specialty Hospital, New Delhi from 2011-2017 to analyze the clinical and epidemiological characteristics of scrub typhus. A total of 41 cases of confirmed scrub typhus and rickettsial infection were included in the study. All patients diagnosed positive for *O. tsutsugamushi* by serological methods (ELISA) were included in the study. Epidemiological and clinical data was extracted from patient files. Information was collated and analyzed using Microsoft Excel (Microsoft Corporation, 2010). The data was statistically analyzed. Quantitative variables were described using frequency and percentages. Maps were prepared using Environmental System Research Institute (ESRI) India's ArcGIS Desktop 10.5 software using shapefiles of localities and zones of Delhi in collaboration with Indian Council of Medical Research (ICMR) and National Institute of Malaria Research (NIMR).

A total of 41 cases diagnosed with scrub typhus and rickettsial infection from 2011 to 2017 were confirmed serologically using ELISA. The age of patients ranged from 10-77 years, with a mean age of 42.3 years. The study participants included 22 (53.7%) males and 19 (46.3%) females.

In India, scrub typhus has been reported from all over India including Shivaliks (Himalayan foothills), Delhi, Haryana, Rajasthan, Maharashtra, Uttarakhand, Chhattisgarh, Kerala, and Tamil Nadu [2]. Figure 1 (a) shows the distribution of total observed scrub typhus cases. The mapping of scrub typhus cases within and around Delhi has been depicted in figure 1(b). In our study, a majority (n = 36; 87.8%) of the cases of scrub typhus and rickettsial infection were reported from Delhi. Other confirmed cases of scrub typhus were reported from Bhutan (n = 1), Gwalior (n = 1), Manipur (n = 1), and Uttar Pradesh (n = 2). Rickettsiosis was seen mostly in Delhi (n = 15), followed by Aligarh (n = 1) and Madhya Pradesh (n = 1). A history of outdoor exposure was seen in 17 out of 41 (41.5%) patients.

Table 1 summarizes the clinical course of scrub typhus among patients. A majority (n = 39/41; 95.1%) of the patients needed hospitalization. The mean duration of hospital stay was 10.05 days, and varied from 2-20 days. Fever was observed in all (100%) cases at the time of presentation. The mean duration of fever prior to hospitalization was 10.7 days. The other most common symptoms reported were shortness of breath (n = 16/41; 39.0%), nausea and vomiting (n = 15/41; 36.6%), abdominal pain (n = 12/41; 29.3%), eschar (n = 11/41; 26.8%, Picture 1) and altered sensorium (n = 11/41; 26.8%). All (100%) patients were administered antibiotics

Figure 1: (a) Distribution of total observed scrub typhus cases (b) Distribution of scrub typhus cases in Delhi.

for treatment. A total of 22 (53.6%) patients were admitted in the intensive care unit (ICU). Death was reported in one (2.4%) case.

Feature	Total cases (N = 41)
Males, n (%) 22	22 (53.7)
Females, n (%)	19 (46.3)
Mean Age (yr)	42.3
Mean hemoglobin (g/dl)	12.03
Hospital Admission, n (%)	39 (95.1)
ICU Admission, n (%)	22 (53.6)
Deaths, n (%)	1 (2.4)
Treatment with antibiotics, n (%)	41(100)
Mean number of days in the hospital (days)	10.05
Mean duration of fever prior to hospitalization (days)	10.7
Clinical Features at presentation, n (%)	
Fever	41 (100)
Cough	6 (14.6)
Shortness of breath	16 (39.0)
Nausea and vomiting	15 (36.6)
Headache	8 (19.5)
Altered sensorium	11 (26.8)
Abdominal pain	12 (29.3)
Oliguria	4 (9.8)
Eschar	11 (26.8)
Icterus	6 (14.6)
Splenomegaly	3 (7.3)
Hepatomegaly	4 (9.8)

Table 1: Clinical characteristics of confirmed scrub typhus cases from 2011-2017.

Picture 1: (a) Characteristic eschar seen on the scrotum (b) Eschar on the thigh, resembling skin burn from a cigarette.

The laboratory parameters of the 41 confirmed cases of scrub typhus and rickettsial infection are presented in table 2. Hematological investigations revealed a hemoglobin <120 g/l in 22% (n = 9) patients. Total Leukocyte Count (TLC) deviated from the normal range in some patients, with leukopenia (TLC < 4×10^9/l) reported in 9.8% (n = 4) cases and leukocytosis (TLC ≥ 11×10^9/l) noted in 34.1% (n = 14) patients. Differential leukocyte count (DLC) values showed neutrophilia and lymphopenia in 46.3% (n = 19) and 80.5% (n = 33) patients, respectively. Platelet count less than 150×10^9/l (thrombocytopenia) was recorded in 31.7% (n = 13) subjects. Biochemical analysis showed high direct bilirubin, elevated Serum Glutamic Oxaloacetic Transaminase (SGOT > 40 U/l), raised Serum Glutamic Pyruvic Transaminase (SGPT > 40 U/l), high Gamma Glutamyl Transferase (GGT >50 U/l), and raised Alkaline Phosphatase (ALP > 90 U/l) values in 87.8% (n = 36), 95.1% (n = 39), 95.1% (n = 39), 63.4% (n = 26), and 63.4% (n = 26) cases, respectively. Hyponatremia (Serum sodium, Na < 135 mmol/l) was seen in 51.2% (n = 21) cases and elevated creatinine levels (> 123.7 µmol/l) were reported in 26.8% (n = 11) cases. Albumin values less than 35 g/l was observed in a majority (n = 37; 90.2%) of the patients. Radiological examination revealed pleural and pericardial effusion in 61.0% (n = 25) and 46.3% (n = 19) cases, respectively. Hepatomegaly was reported in 22.0% (n = 9) cases and splenomegaly in 19.5% (n = 8) cases.

Parameters	No. of cases (%)	Reference range (SI units)
Hematological investigations		
Hemoglobin <110 g/l	9 (22.0)	Males: 120-180 g/l; Females:115-165 g/l
Hemoglobin <80 g/l	1 (2.4)	78-98 fl
Mean cell volume (MCV <80 fl)	4 (9.8)	
Mean cell volume (MCV <60 fl)	3 (7.3)	
TLC <4×10^9/l	4 (9.8)	4.0-11.0×10^9/l
TLC 4-11×10^9/l	23 (56.1)	
TLC ≥11×10^9/l	14 (34.1)	
Differential leukocyte count (DLC):		
Neutrophilia	19 (46.3)	
Neutropenia	2 (4.9)	2.0-7.5×10^9/l
Lymphocytosis	2 (4.9)	
Lymphopenia	33 (80.5)	1.5-4.0×10^9/l
Platelet count <150×10^9/l	13 (31.7)	
Platelet count >150×10^9/l	28 (68.3)	150-350×10^9/l
Biochemical analysis		
High total bilirubin (> 2 µmol/l)	18 (43.9)	2-17µmol/l
High direct bilirubin (> 7 µmol/l)	36 (87.8)	0-7 µmol/l
High SGOT(> 40 U/l)	39 (95.1)	10-35 U/l
High SGPT (> 40 U/l)	39 (95.1)	10-40 U/l
High GGT(> 50 U/l)	26 (63.4)	Males: 10-55 U/l; Females: 5-35 U/l
High ALP(> 90 U/l)	26 (63.4)	40-125 U/l
Albumin (<35 g/l)	37 (90.2)	36-47 g/l
Hyponatremia (Na<135 mmol/l)	21 (51.2)	132-144 mmol/l
Profound hyponatremia (Na<125 mmol/l)	2 (4.1)	
Creatinine >123.7µmol/l	11 (26.8)	55-120 µmol/l
Hypokalemia (K<3.5) mmol/l	7 (17.1)	3.6-5.1 mmol/l
Hyperkalemia (K>5.1 mmol/l)	5 (12.2)	
Radiological Examination		
Hepatomegaly	9 (22.0)	
Splenomegaly	8 (19.5)	
Pleural effusion	25 (61.0)	
Pericardial effusion	19 (46.3)	
Ascites	7 (17.1)	

Table 2: Laboratory and radiologic findings of patients with scrub typhu**s.**

SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; GGT: Gamma Glutamyl Transferase; ALP: Alkaline Phosphatase.

Discussion

Scrub typhus is known to occur throughout India [7]. The epidemiology, clinical presentation, and severity vary according to the geographical area [10]. Scrub typhus outbreaks are seen during the cooler months and after monsoons in South India, whereas in North India it is more commonly seen post monsoons [10].

The epidemiological and clinical features suggestive of scrub typhus in a patient presenting with fever include a history of exposure to the infective agent and presence of an eschar. In our study, none of these were seen in a majority of the cases. The findings are in accordance with a study by Bhargava A., *et al*. [11]. In the present study, the characteristic eschar was seen in 26.8% (n = 11) cases (Picture 1). Bhargava A., *et al*. Rawat V., *et al*. and Kumar M., *et al*. reported eschars in 17%, 4.7%, and 11% cases, respectively [1,10,11].

This study did not report any major complications such as acute respiratory distress syndrome (ARDS), which is consistent with the findings by Bhargava A., *et al*. [11]. A possible reason for this could be the variation based on the vector serotype causing the disease.

In our study, leukocytosis was reported in 34.1% cases, thrombocytopenia was noted in 31.7% patients, elevated liver transaminases were seen in 95.1% cases, and raised GGT and alkaline phosphatase levels were reported in 63.4% cases. Serum creatinine values greater than 123.7 µmol/l were observed in 26.8% patients whereas albumin levels less than 35g/l (hypoalbuminemia) were seen in a majority (90.2%) of the cases. Abnormal elevation in liver transaminases (94.6%), thrombocytopenia (85.7%), elevated bilirubin (33.3%) and serum creatinine (60%) was also seen in a study by Sinha P., *et al*. [12]. Further studies by Kumar M., *et al*. and Bhargava A., *et al*. have shown similar results [1,11]. Our study corroborates these findings.

The present study has certain limitations. This study was based on patients in a tertiary care hospital and could not be considered representative enough for generalizability of results. Moreover, some selection bias may be present as the study was hospital-based. However, the consideration of serologically confirmed cases of rickettsiosis, including scrub typhus, for analysis and the relatively large sample size are the strengths of this study. Further research with a more representative and larger sample size is warranted.

Conclusion

This case series is unique as it provides information on scrub typhus cases prevailing in non-endemic areas which usually go undiagnosed due to a non-specific clinical presentation, lack of awareness and clinical acumen in diagnosing the infection, as well as inadequate laboratory techniques. This study highlights the importance of increasing awareness among individuals and practitioners regarding rickettsioses including scrub typhus. Early intervention based on a combination of clinical, laboratory, and epidemiological evaluation is of paramount importance to arrive at a definitive diagnosis and thereby reduce the morbidity and mortality associated with this disease.

Conflict of Interest

The authors declare that they have no competing interests.

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