Scrub Typhus – A Threatening Scenario in North Bengal

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ABSTRACT

BACKGROUND

Scrub typhus is a mite borne zoonotic bacterial disease caused by *Orientia tsutsugamushi*. It is transmitted by bite of chiggers of trombiculid mite. Clinical features generally include fever, headache, and myalgia, with or without eschar/rash. People with severe illness may develop organ failure and bleeding which can be fatal if left untreated. This study was done to detect outbreak of cases of scrub typhus in Eastern India. These mites generally live in paddy fields of forested area and people visiting those areas are generally affected. Now a days these mites migrate to urban area resulting in increased incidence of scrub typhus infection in urban area. This study was conducted in collaboration with another institute. The purpose of this study was to find out the incidence of scrub typhus in our area and the relationship between occurrence of scrub typhus and seasonal, age and sex variation.

METHODS

This study was carried out in our tertiary care hospital with 441 samples for a period of one year (01.01.2019 to 31.12.19). All the blood samples collected from febrile patients were subjected to Weil Felix test. If the titre is > 1 : 160; this was further confirmed by specific IgM testing. Both Weil-Felix tests and IgM scrub typhus positive tests were noted.

RESULTS

Out of 441 samples, 98 (22.2 %, n = 441) samples were positive for both Weil-Felix and scrub typhus IgM by enzyme linked immunosorbent assay (ELISA) testing. Most of the cases were seen in males. Seasonal distribution showed higher cases in the months of September and October.

CONCLUSIONS

In our study, the highest numbers of scrub typhus cases were found in rural areas, during the harvesting period of July–September specially in monsoon or post monsoon period when there is abundance of mite larva. This infection is also reported high in cases among children in the age group of 1 - 14 years. Patients who tested positive for scrub typhus improved radically with doxycycline.

KEYWORDS

Orientia Tsutsugamushi, Scrub Typhus, IgM ELISA

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BACKGROUND

Scrub typhus is a vector-borne endemic zoonotic infection prevalent in South Asia, Southeast Asia, East Asia, the Pacific Islands, and Northern Australia (the "tsutsugamushi triangle"). Typhus has been derived from Greek word "tŭphos" meaning "fever, stupor" i.e. altered state of mind.[1] This infection is caused by *Orientia tsutsugamushi*, an obligate intracellular parasite of mites belonging to the family Trombiculidae.[2,3] Its genome size is 2.0 - 2.7 Mb. It has the most repeated deoxyribonucleic acid (DNA) sequences among bacterial genomes sequenced so far. As a consequence of this, it has been difficult to generate complete genome assemblies of Orientia using short-read sequencing technologies. Unlike other gram-negative bacteria, it is not easily stained by gram stain due to lack of lipophosphoglycan and peptidoglycan. This bacterium can be antigenically classified by a 56-kDA protein into several subtypes (strains). The classic strains are Karp (causing 50 % of all infections), Gilliam (25 %), Kato (< 10 %), Shimokoshi, Kuroki and Kawasaki.[4] Disease severity also depends upon strain. This bacterium is transmitted to humans by the bite of infected chiggers (larvae) of trombiculid mites.[5] Infection starts when chiggers bite on the skin during their feeding. After inoculation through feeding site, bacteria multiply locally and cause progressive tissue damage (necrosis), which leads to formation of an eschar on the skin. Necrosis progresses to inflammation of the blood vessels (vasculitis) and ultimately causes inflammation of lymph node (lymphadenitis and lymphadenopathy). This vasculitis extends to different organs causing involvement of different organ. Incubation period is 6 - 21 days. Clinical manifestations range from asymptomatic to severe disease. The most characteristic lesion is eschar. This lesion starts from vesicle at the site of bite of mite, ultimately progresses to ulcer having black necrotic center and an erythematous border with regional lymphadenopathy.

This organism mainly affects the vascular endothelium and mononuclear macrophages causing vasculitis. Therefore, all organs, including the lungs, liver, kidneys, and central nervous system, can be affected.[6] Scrub typhus, a zoonotic infectious disease, usually presents with acute febrile illness (AFI) of variable severity. The overall mortality varies from 7 % to 30 %, next only to malaria among infectious diseases.[7] Human beings get infected accidentally when they encroach upon mite-infested rural and suburban areas. It is often acquired during recreational, occupational or agricultural exposure because crop fields are an important reservoir for transmission.[8] The disease can progress to severe complications like acute respiratory distress syndrome (ARDS), hepatitis, acute kidney injury, myocarditis leading to heart failure, and meningoencephalitis in different proportions of the patients. According to the World Health Organization (WHO), a disease outbreak is the occurrence of cases of a disease in excess of what would normally be expected in a defined community, geographical area, or season. Under this definition, a single case of a communicable disease long absent from a population, a disease caused by an agent (for instance a bacterium or virus) not previously recognized in that community or area, or the emergence of a previously unknown disease may also constitute an outbreak. Scrub typhus has been endemic in the Asia-Pacific region, bounded by Japan in the east, Pakistan in the west, Russia in the north and Australia in the south. It accounts for up to 19 % of patients admitted to hospitals with undifferentiated febrile illnesses. Scrub typhus occurred in epidemics among troops in the Myanmar, Sri-Lanka, India and West Bengal during the second world war. During this pre-antibiotic era, mortality rates were as high as 40 – 45 %.[9] This was followed by a marked decline in the number of reported cases in humans, possibly due to the use of tetracycline and chloramphenicol, and pesticides.

O. tsutsugamushi possesses a small genome that has evolved in close association with arthropod hosts; therefore, *O. tsutsugamushi* cells are adapted to survive within the host cells.[10] This obligate, intracellular lifestyle precludes Orientia spp. from being cultivated on agar plates or in broth; instead, the organism is most commonly cultured in eukaryotic host cells within the required confines of biosafety level 3 (BSL3) laboratories. *O. tsutsugamushi* commonly infects endothelial cells, macrophages and polymorphonuclear leukocytes in patients and/or susceptible animals. It can also grow in the yolk sac of 5 – 7 days old embryonated chicken eggs, as well as established cell lines such as L929, Vero, BHK, McCoy and HeLa cells.[11] In addition, *O. tsutsugamushi* may grow in conventional haemocultures for a short time, which can be a useful technique for diagnostic purposes.

Doxycycline is the mainstay of treatment. Previously, chloramphenicol was drug of choice. Although effective, the use of either chloramphenicol or tetracycline poses risks to certain populations (pregnant women and children). Side effects associated with both of these drug classes have been noted in these specific populations. Treatment with either of these drug classes during pregnancy or childhood should be avoided due to risk of teratogenicity.[12] Alternative antimicrobial therapies have been examined for clinical use for this reason. More recently, additional antibiotic classes, such as macrolides, quinolones and rifampicin, have also proven to be effective choices in disease treatment and management, although with varying degrees of effectiveness.[13,14]

However, in the 21st century, we have seen the emergence of a major health care issue evident across the globe: serious infections caused by bacteria that have become resistant to commonly-used antibiotics.[15] Previously reliable treatments for many bacterial agents have become ineffective with the increasing rate of antibiotic resistance, as well as the emergence of 'superbugs' (dangerous multidrug-resistant strains),[16] making this an area of increasing concern. Nowadays there is emergence of doxycycline resistant *Orientia tsutsugamushi* which is responsible for drug failure.

Antigenic variation is of major concern for vaccine development against scrub typhus. Immunity to one strain does not confer protection to another strain. From 1945, researchers tried to prepare vaccines (injectable, subunit, DNA) which will be effective for control of epidemic. As there is no vaccine against scrub typhus till now, source reduction,

personal protection and chemoprophylaxis are still effective in controlling this infection. Although this infection is common in northern India but is often under diagnosed or neglected. In India there were several outbreaks of this infection in different states. But in our North Bengal, actual scenario is not known. So, this study is an effort to find out actual incidence of scrub typhus in our area.

Objectives

1. To find out the incidence of scrub typhus in our area.
2. To find out relationship between occurrence of scrub typhus and variation of age, sex and environmental temperature.

METHODS

This study was carried out in a tertiary care hospital in the department of microbiology for a period of one year. All clinically suspected patients with an acute febrile illness (in whom malaria, leptospirosis, dengue fever, viral pharyngitis, enteric fever and urinary tract infection were excluded by history, clinical examination and appropriate laboratory investigations) were included in this study. During this one-year study period, a total of 441 blood samples were received. A detailed history was collected and a thorough physical examination was carried out. All patients were managed according to the standard protocols as advocated by the surviving sepsis campaign guidelines.

The patients with bilateral chest infiltrates on a chest X-ray, a ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (PaO_2/FIO_2) < 300 in the absence of heart failure were defined as ARDS. Multiple organ dysfunction syndrome (MODS) was confined to acutely ill patients presenting with features of two or more altered organ system functioning. Laboratory tests carried out were complete blood count (CBC), renal function tests (RFT), liver function tests (LFT), coagulation tests including international normalized ratio (INR) and activated partial thromboplastin time, serum electrolytes, calcium, and phosphorous.

Tests carried out as a workup for infectious diseases were blood culture, urine examination and culture, rapid tests for dengue, rapid antigen test and smear examination for malaria, and Widal test. IgM serology using commercial enzyme-linked immunosorbent assays were performed for leptospirosis. Blood samples from suspected febrile patients were tested for the presence of non-specific anti-rickettsial antibodies by using OX 19, OX2 and OXK strains of Proteus species (Weil-Felix test). IgM ELISA test detects IgM antibody against *O. tsutsugamushi*. All demographic data, detailed history, past treatment history/any comorbid illnesses were recorded in a proforma. A complete physical examination, vital signs and relevant investigations were also noted.

Inclusion Criteria

1. Pyrexia for more than 5 days.
2. Positive serology for scrub typhus.

Exclusion Criteria

1. Patients with other established causes of pyrexia other than scrub typhus such as malaria, dengue, leptospirosis, enteric fever, and viral meningitis.
2. Negative serology for scrub typhus.
3. Incomplete case records.
4. Patient refusal to participate in the study.

Weil-Felix test was performed by using proteus antigen and subsequently scrub typhus serology was tested in batches for IgM antibodies to *Orientia tsutsugamushi* using commercial enzyme-linked immunosorbent assay kits (Panbio Ltd, Brisbane, Australia). The kit uses a specific 56 kDa recombinant antigen of *O. tsutsugamushi* and has a sensitivity and specificity of > 90 % when compared with recommended gold standard tests, namely the immunofluorescent antibody (IFA) and indirect immuno-peroxidase tests. The test was performed as per manufacturer's instructions. A diagnosis of scrub typhus was confirmed when a patient with an AFI had a positive serology for scrub typhus, further strengthened by either the presence of eschar or exclusion of other causes of fever.

Statistical Analysis

Statistical analysis was made by using Statistical Package for Social Sciences (SPSS) software.

RESULTS

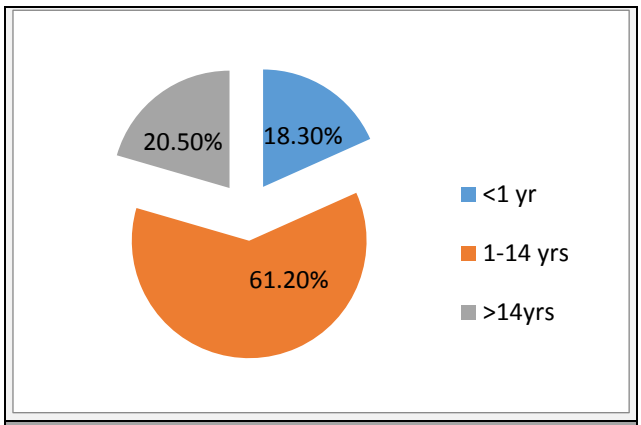
Total number of patients: 441
Total number of positive scrub typhus patients: 98
Total number of negative patients: 343
Total number of deaths: 6 (6.1 %, n = 98).
Death occurred due to mainly pneumonia [2 (33.6 %)], myocarditis [1 (16.6 %)] and meningoencephalitis [3 (50 %)].

Total Cases	Positive	Negative	% of Positive Cases
441	98	343	22%

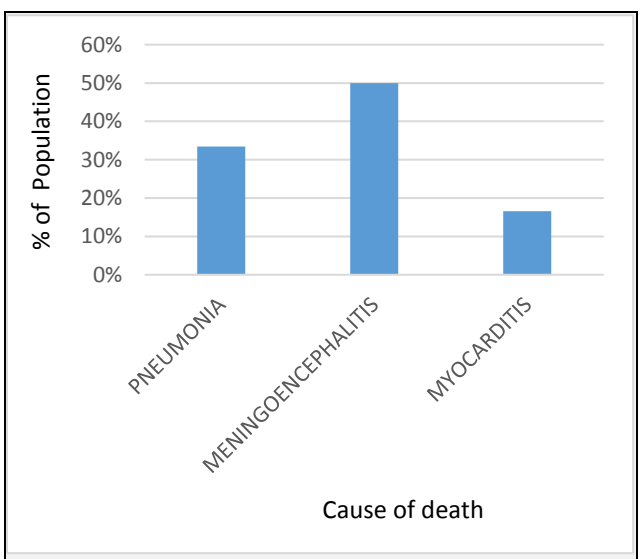
Table 1. Percentage of Positive Population (22 %, n = 441)

Fever with chill and rigor	441 (100 %)
Shortness of breath or respiratory distress	198 (45 %)
Cough with bleeding	238 (54 %)
Eschar	61 (14 %)
Diarrhoea	152 (34.4 %)
Lymphadenopathy	154 (35 %)
Myalgia	396 (90 %)
Jaundice	29 (6.5 %)
Altered sensorium	52 (12 %)
Hypotension	30 (6.8 %)
Hepatomegaly	104 (23 %)
Splenomegaly	101 (22.9 %)
Pneumonitis	28 (6.3 %)
Oliguria	10 1(23 %)

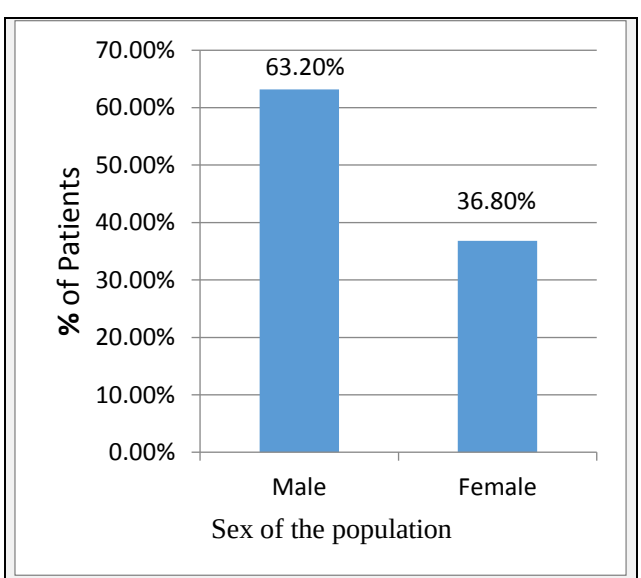
Table 2. Distribution of Scrub Typhus According to Clinical Feature. Most Common Symptoms of Patients Were Fever, Breathlessness, Coughing Out of Blood



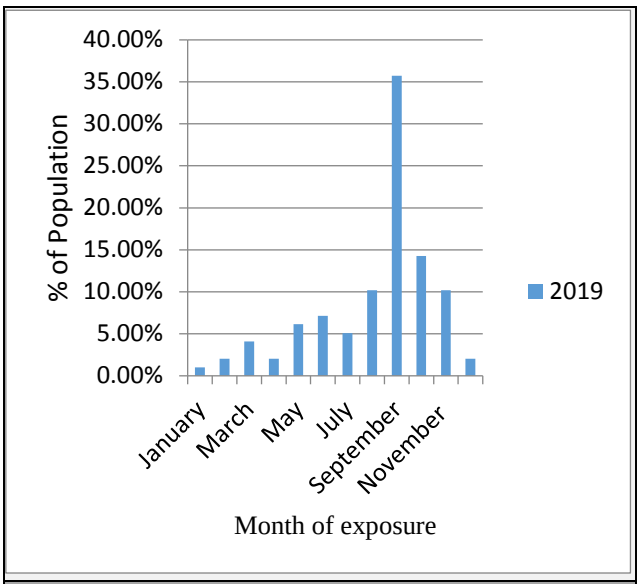
Pie Diagram 1. Distribution of Scrub Typhus Positivity According to Age. Most Commonly Disease Occurred in between 1 to 14 Years Old Children



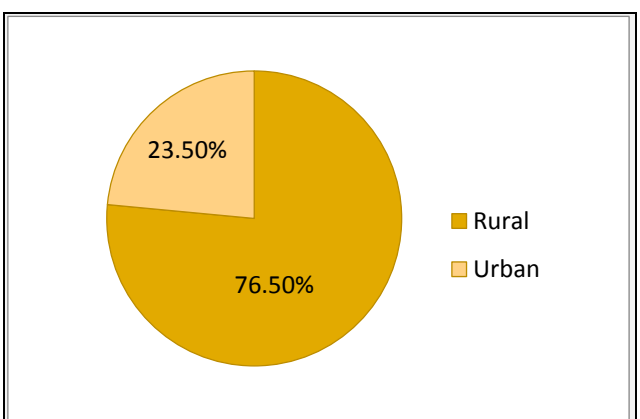
Column 1. 50 % of Death Occurred Due to CNS Complications like Meningitis and Meningoencephalitis.



Bar Diagram 1. Distribution of Positive Case According to Sex. (63.2 % = male), (36.8 % = female)



Bar Diagram 2. Season Wise Distribution of Scrub Typhus Positivity. Infection Occurred Maximally from August to November Month



Pie Diagram 2. Area Wise Distribution of Scrub Typhus Positive Case. Rural Area has Higher Vegetations and Also has Favourable Temperature and Humidity Required for Growth of Mites

DISCUSSION

Orientia tsutsugamushi, the causative agent, has > 20 antigenically distinct serotypes due to a wide variation in the antigenic protein –56 kDa TSA which is the most abundant protein of Orientia genus.[17] *Orientia tsutsugamushi* is an obligate intracellular, gram-negative bacterium causing scrub typhus. The chigger mites of the family Trombiculidae of genus *Leptotrombidium* are responsible for the disease transmission.[18] The so-called "tsutsugamushi triangle" region, which extends from northeast Asia to Papua New Guinea and northern Australia in the southeast, Pakistan and Afghanistan in the northwest, and the Maldives and Réunion Islands in the southwest, is endemic for scrub typhus with around 2 million of the population at risk.[19,20] In India this infection is present in Kashmir to Assam, Eastern and Western Ghats and the Satpura ranges in the central part of India. There has been reported case of emerging and remerging infection in India. There were several reports of scrub typhus outbreak in Himachal Pradesh, Sikkim and

Darjeeling during 2004 - 2007. This disease is highly prevalent in rural workers, adults involved in agriculture, forest occupation, soldiers in temporary camps, and in those living close to bushes and wood piles.

Orientia tsutsugamushi can survive in the host cell by evading the host immune reaction. Once it interacts with the host cells, it causes host cell membrane to form a transportation bubble called a clathrin-coated vesicle by which it gets transported into the cytoplasm. Inside the cytoplasm, it makes an exit from the vesicle (now known as an endosome) before the endosome is destroyed (in the process of cell-eating called autophagy) by the lysosomes. It then moves towards the nucleus, specifically at the perinuclear region, where it starts to grow and multiply.

The clinical presentation of scrub typhus ranges from subclinical disease to multiorgan failure and death. The disease usually presents with fever, diffuse lymphadenopathy, myalgia, rash, jaundice, thrombocytopenia, capillary leak syndrome, hepatomegaly, and splenomegaly. If this disease remains untreated for prolonged time, it may cause serious complications like pneumonia, myocarditis, and meningitis. The CNS manifestations vary from aseptic meningitis to meningo-encephalitis. Patients present with fever, headache, photophobia, confusion, delirium and may develop seizure. Cerebrospinal fluid (CSF) picture mimics viral or tubercular aetiology. Pulmonary manifestations include bronchitis and interstitial pneumonia that may lead to ARDS. ARDS like picture is very rare whereas cough is main symptom. Chest X-ray may show pneumonic change or may be normal. Pulmonary vasculitis is mainly responsible for various lung manifestations. Liver injury is mild ranging from jaundice and abnormal LFT report. Altered serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase and bilirubin are the main LFT features. Sinusoidal infiltration, pericholangitis and perivascular lesion around portal area is responsible for hepatic manifestation. Acute kidney injury is mainly due to pre renal azotaemia. Azotaemia occurs due to hypovolemia. Another cause is due to acute tubular necrosis due to renal vasculitis. Mortality is due to various factors like pathogenic strain, circulatory load of *O. tsutsugamushi*, early or late presentation, treatment modality, drug resistance, geographical region and host factor such as age, immune status and co-morbidities of host and death rate is high in case of diagnosis delay and antibiotic resistance.

In this study, we have seen that 22 % of cases (n = 441) (Table-1) were scrub typhus positive. Majority of these positive cases were among 1 - 14 years of children (Pie diagram - 1). Mainly presented symptoms were fever (100 %), muscle pain (90 %) haemoptysis (54 %), breathlessness (45 %), lymphadenopathy (35 %), eschar (14 %), altered sensorium (12 %) and oliguria (23 %) (Table-2). Death occurred in 6 % cases only and maximally due to meningitis and meningoencephalitis. (Column-1). Maximum number of infection was reported from rural area of Uttar Dinajpur (Pie diagram-2) and specially in monsoon time and just after monsoon (Bar diagram-2). This is attributable to the abundant vegetation growth, increased occupational exposure due to the concurrent harvesting season, leading to more people in the fields and for longer periods of the day in the rainy season.

There are very few published articles regarding scrub typhus. One such study in the year 2005 published by G.M. Varghese showed scrub typhus positivity rate 24.1 % (n = 207). They also showed that elevated creatinine level was an independent predictor of mortality. [21]

According to another study Rajendra Prasad Thakur et al. showed mortality rate of 21.2 % than our study (6 %) and also than other study done by Mahajan et al. (mortality rate 14.2 %).[22,23] This mortality rate also depends upon individual strain. Strain typing is not done in our tertiary care hospital.

CONCLUSIONS

Scrub typhus and rickettsial diseases have long plagued both civilian and military populations throughout the world. Currently, scrub typhus outbreaks are being reported both within the known area of endemicity, as well as beyond the originally defined borders of the Tsutsugamushi triangle. More concerning is the recognition of diseases caused by *O. tsutsugamushi* and other Orientia species far beyond the endemic region (Middle East, Africa, South America). Adding to this concern is the emergence of antibiotic-resistant strains of Orientia species, which can make treatment difficult or unsuccessful, even in the most well-equipped medical/laboratory facilities. Scrub typhus should always be considered in all cases with febrile illness even in the absence of eschar. Preventive measures such as i) maintaining adequate personal hygiene ii) control of rodent population, iii) vector reduction and vegetation control, iv) avoiding travel to regions where typhus exposure has occurred, v) chemoprophylaxis with doxycycline.

This study involved an extensive search of the literature and includes up-to-date and relevant studies. However, there are some limitations:

1. Specific difficulties relating to the diagnosis of scrub typhus - as many patients do not present with specific symptoms and signs like eschar.
2. Misdiagnosis or delayed diagnosis - This is due to those patients who do not seek medical attention in proper time.
3. Majority of fever studies suffer from selection bias and often relies on suboptimal diagnostic tools.

As this disease is commonly accounted as ignorable disease, close suspicion of the disease along with the increased use of affordable and accurate rapid tests, treatment of positive case with antibiotics can easily prevent fatal outcome.

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