Scrub Typhus: Re-emerging Public Health Problem in India

Ananya Ray Laskar*, Shivali Suri**, Anita Shankar Acharya***

Abstract

Scrub Typhus is emerging as an important cause of fever of unknown origin and needs to be differentiated from other causes of febrile illnesses. During March to June 2014, a systematic search on ‘Scrub typhus’ was conducted to determine epidemiology and factors causing re-emergence of this disease in India. Scrub typhus is an acute, febrile, infectious illness caused by Orientia tsutsugamushi, transmitted to humans through bites of the trombiculid mites. The infection can range from a mild, self-limiting disease to a fatal illness in 35-50% of cases, with multi-organ dysfunction, if not promptly diagnosed and appropriately treated. The reports of the disease were rare for several decades, but currently a clear re-emergence has been documented from several states in India. This resurgence may be attributed to changes in the human behavior-unplanned urbanization, deforestation and rapid transport leading to displacement of vectors as well the rodents from one place to another. There is an urgent need for awareness generation among the medical and para-medical professionals especially at the peripheral levels. Standard treatment guidelines for timely diagnosis and treatment of Scrub Typhus should be available, especially in rural areas, where the disease remains undiagnosed, and this should be in accordance with the facilities available at sub-centers, PHCs, and CHCs. Active surveillance of rickettsial diseases is required to be carried out to know exact magnitude and distribution of the disease.

Keywords: Fever, Mite, India, Scrub typhus, Tsutsugamushi.

Introduction

Scrub typhus (also known as tsutsugamushi disease, mite-borne typhus, Japanese-river fever, tropical typhus) is an acute, febrile, infectious illness caused by Orientia tsutsugamushi, previously categorized in the Rickettsia genus, and is transmitted to humans through bites of infected larval stage (chigger) of the trombiculid mites. The pathogen on entering the human body, begins to proliferate at the site of bite and a characteristic necrotic skin lesion, known as an eschar, is formed. It then spreads systemically via the hematogenous and lymphogenous routes and the infected people develop various systemic symptoms and reactions including fever, cutaneous rash, myalgia, and lymphadenopathy. However, the vast variability and non-specific presentation of this disease often makes it difficult for the clinicians to diagnose.

Methodology

During March to June 2014, we conducted a systematic search by collecting scientific research articles on ‘Scrub typhus’ from medical libraries and through Pubmed, Google scholars, PLOS, Google, Index Copernicus and MedlinePlus using key-words like Scrub Typhus, India, ecological factors, urban areas, laboratory diagnosis, treatment. We also visited the websites of CBHI and IDSP to determine the outbreaks of Scrub typhus cases over the past 10 years.

Epidemiology of the Disease

Scrub typhus is endemic to a part of the world known as the “tsutsugamushi triangle” which extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west.

*Assistant Director, National Centre for Disease Control.
**Senior Resident, Department of Community Medicine, Lady Hardinge Medical College & Associated Hospitals.
***Professor, Department of Community Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi-11000, India.

Correspondence to: Dr Anita Shankar Acharya, Professor, Department of Community Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi-11000, India.

E-mail Id: anitaacharya29@gmail.com

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The causative organism, *Orientia tsutsugamushi* infects various cells, including endothelial cells and phagocytes, causing acute vasculitis. It exhibits genetic, antigenic and pathogenic diversity with numerous serotypes recognized. Even though it is recognized as one of the tropical Rickettsial diseases, *O. tsutsugamushi* has a different cell wall structure and genetic composition than that of the rickettsiae. Endemic foci occur in areas undergoing ecological transition such as abandoned farmland or human made forest clearings, serving as ideal living conditions for the host of mites. Cases of scrub typhus most frequently occurred among farmers, forestry workers, and others involved in outdoor occupations. However, it was also diagnosed in urban areas with no history of exposure to reservoir.

It is transmitted to humans through bites of infected larval stage (chigger) of the trombiculid mites. The incubation period of scrub typhus is about 5 to 20 days (mean 10-12 days) after the initial bite. The chigger mites feed on small mammals like rodents, field mouse, rats, squirrels and bandicoot. The mite is very small (0.2-0.4mm) and can only be seen through a microscope or magnifying glass. The mites act as both vectors and reservoir due to trans-ovarial transmission of *O. tsutsugamushi*. Hence, once they are infected they maintain the infection throughout their life stages and, as adults, pass the infection on to their eggs. Humans are accidental hosts in this zoonotic disease. No person to person transmission has been documented.

The trombiculid, during their larval stage (chiggers), feed on skin cells of animals and human beings, by making holes in the skin. The larvae bite causes severe itching and lesions. The larva becomes harmless when it matures and becomes an adult.

The disease is mostly reported during the monsoon and post-monsoon when there is a spurt in dengue, malaria and viral fever-all with similar symptoms. Majority of the cases occur after rainy season in July-August and continue through winter. The knowledge of the meteorological factors may be useful for prediction of an epidemic and development of an early warning system through implementation of preventive public health interventions.

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<th>Study (Year)</th>
<th>Region</th>
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<td>Sharma A et al. (2005)</td>
<td>Himachal Pradesh</td>
<td>Males (40%)</td>
<td>Fever (100%), lymphadenopathy (44%), splenomegaly (37%), eschar (5.8%)</td>
<td>Weil felix test</td>
<td>Abnormal Liver Function Tests (28%)</td>
<td>Pneumonitis, encephalitis, acute renal failure</td>
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<td>Mahajan S.K. et al. (2006)</td>
<td>Himachal Pradesh</td>
<td>Males (61%)</td>
<td>Fever (100%), Chills, rigor (71.4%), Lymphadenopathy (52.3%), Vomiting (42.8%), Eschar (9.5%)</td>
<td>Polymerase Chain Reaction (PCR), Weil-Felix assay, microimmunofluorescence assay</td>
<td>Elevated transaminase (66.7 %), Renal dysfunction (66.7%), Proteinuria (38.1%)</td>
<td>Acute respiratory distress syndrome (ARDS), Renal complications</td>
</tr>
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<td>Vivekanandan M et al. (2010)</td>
<td>Pondicherry</td>
<td>14-91 years Males (44%)</td>
<td>Fever (100%), Nausea, vomiting (58%), headache (52%), eschar (46%)</td>
<td>Weil Felix test</td>
<td>Elevated transaminases (95.9%), raised bilirubin (20.5%), renal failure (13%)</td>
<td>ARDS, Shock, Meningitis, Renal impairment</td>
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<tr>
<td>Varghese GM et al. (2013)</td>
<td>Vellore</td>
<td>46±15 years/ Males (54 %)</td>
<td>Fever (100%), Shortness of breath (57.7 %), Nausea/ vomiting (54.2%),</td>
<td>PCR, IgM ELISA,</td>
<td>Elevated transaminase, (72.5%), Elevated bilirubin (26.6%)</td>
<td>ARDS, Shock, hepatitis, renal impairment/ Case fatality (7.8%)</td>
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Table 1. Major epidemiological features of diagnosed cases of Scrub Typhus in various studies conducted in India

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<th>Study</th>
<th>Location</th>
<th>Age/Males</th>
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<tr>
<td>Prakash A et al. (2013)</td>
<td>Delhi</td>
<td>28-55 years Males (25%)</td>
<td>Fever (100%), respiratory symptoms (75%), GIT symptoms (75%), eschar (100%)</td>
<td>IgM ELISA</td>
<td>Elevated transaminases, renal dysfunction, leukocytosis, Jaundice, Renal failure, Pneumonitis, ARDS</td>
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<td>Vivek Kumar et al. (2014)</td>
<td>Foot hills of Himalayas</td>
<td>34.1±14 years Males (59%)</td>
<td>Fever (98%), Shortness of breath (67%), Eschar (18%)</td>
<td>PCR, IgM ELISA</td>
<td>Renal abnormalities (82%), Elevated transaminase, Hepatic dysfunction, thrombocytopenia, Shock, ARDS, Acute Kidney Injury</td>
</tr>
<tr>
<td>Singh SP et al. (2014)</td>
<td>Uttarakhand</td>
<td>Males (55%)</td>
<td>Fever (100%), Myalgia (80%), Headache (74%), Eschar (0%)</td>
<td>IgM ELISA</td>
<td>Elevated transaminase (79%), thrombocytopenia (47%), renal dysfunction, ARDS, renal failure, hepatitis, Meningoencephalitis, shock/Case fatality (6.4 %)</td>
</tr>
<tr>
<td>Varghese GM et al. (2014)</td>
<td>Vellore</td>
<td>45 ±15 years Males (48%)</td>
<td>Fever (100%), Nausea/vomiting (54%), Shortness of breath (49%), Headache (46%), Eschar (43.5%)</td>
<td>IgM ELISA, PCR</td>
<td>Elevated transaminases (87%), thrombocytopenia (79%), leukocytosis (46%), ARDS, Shock, Hepatitis, Meningoencephalitis, Case-fatality (9.0%)</td>
</tr>
</tbody>
</table>

Clinical Presentation

The vast variability and non-specific presentation of this infection have often made it difficult to diagnose it clinically. The infection can range from a mild, self-limiting disease to a fatal illness in 35-50% of cases, with multi-organ dysfunction, if not promptly diagnosed and appropriately treated.

After a variable incubation period of 7-21 days, acute fever is the most common presenting symptom, often associated with rigors, chills, breathlessness, regional lymphadenopathy, cough, nausea, vomiting, myalgia, and headache. Since clinical presentation of fever with rash and myalgia occurs in other febrile illnesses like dengue fever, malaria and typhoid; they should be considered in differential diagnosis. A maculopapular rash may appear at the end of first week, first on the chest, abdomen and trunk and then on proximal extremities.

An eschar at the bite site of the mite is pathognomonic of Scrub typhus. On careful examination, papule may be seen at the site of inoculation which ulcerates and eventually heals with the development of a black eschar. A significant difference exists in the distribution of eschars. The common locations of eschar range from chest, nape of neck, arm, index finger of hand, hypogastric region, gluteal region and popliteal fossa. An eschar may be a highly variable finding, found in anywhere from 10% to 92% of patients with scrub typhus, but may not be found, even when present, unless thoroughly
searched for. The non-specific presentation and lack of the characteristic eschar patients makes the misdiagnosis and underreporting of scrub typhus common.\textsuperscript{15}

Common laboratory findings show diversity and commonly include elevated transaminases, thrombocytopenia, leukocytosis, renal dysfunction, hepatic abnormality, and proteinuria.

**Complications**

The patients infected with Scrub typhus may succumb to complications if not promptly diagnosed and appropriately treated. Systemic complications commonly reported as causes of death include respiratory, cardiovascular, renal, hepatic, central nervous system or multiple-organ involvement. Severe complications, including acute respiratory distress syndrome (ARDS), shock, hepatitis, renal failure, meningoencephalitis, and myocarditis, may occur in varying proportions of patients.\textsuperscript{3}

**Diagnostic Tests in India**

Accurate and early diagnosis of scrub typhus remains a challenge in India because of its nonspecific presentation and the paucity of confirmatory diagnostic resources. Diagnostic tests such as the Weil-Felix agglutination test are very insensitive and non-specific.\textsuperscript{3} Weil Felix test detects IgM antibody which is detectable 5-10 days following the onset of symptoms. The test results may be negative during the early stages of the disease because the agglutinating antibodies are detectable only during the second week of illness.\textsuperscript{17}

The serologic diagnosis can be done with IgM ELISA testing. ELISA, when performed with 56 KDa antigen, has 90\% sensitivity and specificity, allows detection of IgG and IgM antibodies, and provides positive results within 3-4 days after the onset of illness. However, it has limited availability in the government medical colleges.\textsuperscript{3}

The isolation of the organisms in animals or cell culture is limited by the lack of containment facility as well as the lack of expertise in handling these high risk group pathogens. Moreover, isolation is time consuming, tedious and requires a BSL3+ facility.\textsuperscript{8}

The gold standard test for the serologic diagnosis of scrub typhus is the immunofluorescence assay (IFA). However, while sensitive, the IFA is expensive, requires specialized labs and considerable training. The immunochromato graphic test (ICT) to detect antibodies against \textit{O. tsutsugamushi} was introduced as a rapid diagnostic test.\textsuperscript{16}

Eschar samples can be used for conducting Polymerase Chain Reaction. Bacterial DNA is used as the template for the PCR and a standard PCR targeting the 56-kDa protein can be carried out.\textsuperscript{3}

**Treatment**

Scrub typhus is an easily treatable disease and deaths can be averted through use of antimicrobials. The recommended treatment for uncomplicated cases is Doxycycline 100mg twice daily for 7-15 days or Chloramphenicol 500mg four times a day for 7-15 days which is cost-effective. In children, dose of Chloramphenicol is 150mg/kg for 5 days. If treatment is not initiated, fever and other symptoms may persist for more than three weeks. If resistant to Doxycycline, a single dose of 500 mg of Azithromycin has been found to be effective. However, cases must be suspected earlier based on clinical findings and a delay of more than two weeks may lead to severe form of the disease.\textsuperscript{6,7}

For travelers, personal prophylaxis with protective clothing, treatment of clothing with insecticides and application of mite repellents like DEET to skin are useful. Prophylactic use of Doxycycline at a weekly dose of 200 mg for short term exposures has shown to be effective. Currently, effective vaccination approaches for dealing with scrub typhus are still not available.\textsuperscript{2}

**Re-Emergence of Scrub Typhus in India**

Many studies done in the 1960s and 1970s have demonstrated the endemic nature of this disease in many parts of India. However, in later years, the disease virtually disappeared and was lost from the radar of the scientific community until recently, probably because of widespread use of insecticides to control other vector-borne diseases, empiric treatment of febrile illnesses with tetracyclines and chloramphenicol by medical practitioners, and changes in lifestyle. However, now there seems to be a resurgence and reemergence of the disease in India.\textsuperscript{13}

Earlier, the habitat of the mite was restricted to the shrubs in hilly and forest terrains. But recent studies have shown that rodents carrying the mite are transmitting the disease in the urban locales as well. This resurgence may be attributed to changes in the human behavior-unplanned urbanization, deforestation and rapid transport leading to
displacement of vectors as well rodents from one place to another. An entomological survey conducted in Delhi revealed that poorly maintained kitchen garden and long grass attracted rodent population. Human host in urban areas may get bitten by the disease-causing mite while jogging in parks, doing yoga or any other recreational activities such as camping in the jungles.\(^{17}\)

Scrub typhus was earlier known to be prevalent in the foothills of Himalayas viz. Jammu & Kashmir, Himachal Pradesh, Sikkim, Manipur, Nagaland, Meghalaya, Assam and West Bengal. Few cases were also being reported from Tamil Nadu and Kerala. However, currently samples are being tested positive from Delhi, Chandigarh, Haryana, Rajasthan, Maharashtra, Uttar Pradesh, Uttarakhand and Chhattisgarh.\(^{18}\) The National Center for Disease Control (NCDC) formerly National Institute of Communicable Disease, has played an important role in providing serological evidence of rickettsial diseases in India in the last decade.

The reports of the disease were rare for several decades, but currently a clear re-emergence has been documented from several states in India, including Himachal Pradesh, Tamil Nadu, Kerala, Maharashtra, Bihar, Karnataka, Jammu and Kashmir, Uttarakhand, Rajasthan, West Bengal, and Meghalaya.\(^{1,13,19}\)

Integrated Disease Surveillance Project, which reports outbreaks of scrub typhus in various places of India, shows that during 2005-2013, yearly an outbreak was reported from Nagaland (2005), Manipur (2006), Uttarakhand (2008), Meghalaya (2009), and Assam (2010). Thereafter, the number of outbreaks reported increased to 4; 1 each in Himachal Pradesh, Karnataka, Nagaland and Uttarakhand (2011), which increased to 9, 1 each in Arunachal Pradesh, Himachal Pradesh, and Uttarakhand, and 2 each in Tamil Nadu, Rajasthan and West Bengal (2012), which dropped to 5-1 in Andhra Pradesh, 2 each in Odisha, and West Bengal (Fig. 1).\(^{20}\)

![Figure 1. IDSP reported outbreaks of scrub typhus (2005-2013)](image)

Precise data on the incidence of Scrub Typhus in the past is not available in our country since it was based on non-specific diagnostic techniques like clinical examination and Weil-Felix test. However, due to improved diagnostic techniques, Scrub typhus has now been reported from various parts of India, and has recently been identified as one of the important neglected zoonoses of public health importance.\(^{7}\)

During 2012, outbreaks of Scrub Typhus have been reported from many states of India. The National Center for Disease Control at its Zoonotic division received 742 samples from suspected cases of scrub typhus from 11 states and 202 (27%) were found positive. In 2011, the number of samples received was 484, and in 2010, it was 204 as depicted in Fig. 2.
Conclusion and Recommendations

Scrub typhus is a serious acute febrile illness associated with significant morbidity and mortality. Rickettsial infections should be considered as an important cause of FUO and be included in the list of differential diagnosis of FUO. A high index of suspicion is needed in patients presenting with fever especially during monsoon and post monsoon season. There is an urgent need for awareness generation among the medical and para-medical professionals especially at the peripheral levels.

Due to paucity of resources, the cases of scrub typhus remain under-reported, especially in rural areas. The reported cases of Scrub typhus may in fact be the tip of the iceberg and the immense burden due to it may have still been unrecognized. Hence, it is recommended that standard treatment guidelines for timely diagnosis and treatment of Scrub Typhus should be made available in rural areas which should be in accordance with the facilities available at sub-centers, PHCs, and CHCs. Active surveillance of rickettsial diseases is required to be carried out to know exact magnitude and distribution of the disease. Further, entomological and epidemiological studies for ricketttsioses may be conducted to provide a clear profile of this disease.

References
