Seroprevalence of **Scrub typhus** among Febrile Patients in a Tertiary Care Hospital in Thiruvananthapuram, Kerala

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Abstract

**Scrub typhus** is a rickettsial infection caused by *Orientia tsutsugamushi* that belongs to the family Rickettsiaceae and transmitted by some species of trombiculid mites "chiggers", particularly a *Leptotrombidium deliense*. A necrotic eschar at the inoculating site of the mite is pathognomic of **Scrub typhus**. **Scrub typhus** is a zoonosis and is a widespread disease in Asia and Pacific Islands. Fever is the most common symptom of **Scrub typhus** and in endemic areas; it is one of the causes of fever of unknown origin. In order to understand the clinical spectrum and its prevalence, a retrospective study was conducted in patients admitted with acute febrile illness in Govt. Medical College, Thiruvananthapuram over a period of 1 year. A total of 1268 serum samples were screened for **Scrub typhus** by IgM enzyme-linked immunosorbent assay. About 217 patients were positive among which 118 were male and 99 were female. The seroprevalence of **Scrub typhus** was 17.11%. There were antigenic cross reaction with IgM leptospirosis for 11 cases and IgM dengue for 2 cases. Effective management and early administration of antibiotics will help to prevent the complications and mortality associated with **Scrub typhus**.

Keywords: *Orientia tsutsugamushi*, chiggers, *Leptotrombidium deliense*, eschar, zoonosis.

Introduction

**Scrub typhus** is a re-emerging zoonotic bacterial infection known as the ‘tsutsugamushi triangle’ of South and Southeast Asia, the Asian Pacific rim and Northern Australia. The infection is called **Scrub typhus** because it generally occurs after exposure to areas with secondary (scrub) vegetation. It is an obligate intracellular bacterium that infects various cells including endothelial cells and phagocytes, causing vasculitis. The organisms proliferate on the endothelium of small blood vessels releasing cytokines which damage endothelial integrity, causing fluid leakage, platelet aggregation, leading to the formation of microinfarcts (Rajapakse et al., 2011). After incubation period of 10 to 12 days fever, headache, myalgia, cough and gastrointestinal symptoms develops. The clinical manifestations can range from sub-clinical disease to multiorgan failure. A necrotic eschar at the inoculating site of the mite is pathognomic of **Scrub typhus**. The chigger bite is painless and may become noticed as a transient localized itch. **Scrub typhus** is usually associated with rash, myalgia and diffuse lymphadenopathy. The classic features include an eschar at the site of chigger bite, regional lymphadenopathy and a maculopapular rash. Eschar is usually seen in axilla, groin, neck and inguinal region. The eschar begins as a small papule that enlarges, undergoes central necrosis, and eventually acquires a blackened crust with an erythematosus halo that resembles a cigarette burn. Eschar can cause various complications like jaundice, renal failure, pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and meningoencephalitis. **Scrub typhus** should be differentiated from malaria, dengue, leptospirosis and typhoid fever. The clinical manifestation of leptospirosis and **Scrub typhus** are non-specific and both diseases will present as fever, headache, skin rash, myalgia and conjunctival congestion. The presentation of **Scrub typhus** can be variable, often non-specific, but with potentially severe multiorgan dysfunction. Leukopenia and abnormal liver function tests are commonly seen in the early phase of the illness. Pneumonitis, encephalitis, and myocarditis occur in the late phase of illness (Sindhura et al., 2014). The Well-Felix agglutination test is helpful in establishing presumptive diagnosis of diseases caused by members of typhus and spotted fever groups of Rickettsiae. **Scrub typhus** can be a very serious infection that often presents with non-specific symptoms, making it difficult to differentiate from other infections. History of mite bite is often absent since the bite does not inflict pain and the mites are almost microscopic to be seen by a naked eye. The gold standard test is indirect immunofluorescence, but the main limitation of this method is the availability of fluorescent microscopes (Bhutia and Pradhan, 2013). It is now known that there is enormous antigenic variation in *Orientia tsutsugamushi* strains and immunity to one strain does not confer immunity to another strain. Against these backdrops, this study investigated the seroprevalence of **Scrub typhus** among febrile patients in a tertiary care hospital in Thiruvananthapuram, Kerala.
Materials and methods

Study population and study settings: This study was done over a period of 1 year in the Govt. Medical College, Thiruvananthapuram, Kerala who are presented with an acute febrile illness. All cases of febrile illness diagnosed as Scrub typhus over a period of 1 year were analyzed. Diagnosis was based on the presence of the eschar and positive IgM ELISA. The IgM ELISA test was used for the qualitative detection of IgM antibodies in human serum to Orientia tsutsugamushi derived recombinant antigen which is coated inside the wells of Elisa plate. ELISA test for detection of IgM antibodies is evaluated and found to be satisfactory in comparison to the gold standard. The positive test result can be used as a presumptive diagnosis of Scrub typhus and requires clinical confirmation.

Result

A total of 1268 samples presented with an acute febrile illness were screened for Scrub typhus. About 217 patients were positive among which 118 were male and 99 were female. Table 1 shows the month-wise analysis of the febrile cases and Scrub typhus positive cases. It showed that Scrub typhus positive cases were more in October to January. Table 2 shows that out of the 217 Scrub typhus positive cases, there were 118(54.3%) male and 99(45.7%) female. The ratio is 1.2:1. Adult male were mainly affected. Table 3 shows the age-wise distribution of Scrub typhus positive cases. Most common age group affected was 51-60(21.6%) years, followed by the age group of 41-50(18.9%) years. Children less than 10 years were also affected more. Table 4 shows the clinical features of Scrub typhus. Common symptoms were high grade fever of 7-14 days duration, nausea, vomiting, headache etc. Clinical symptoms associated with Scrub typhus are mainly headache [116(53.4%)], nausea, vomiting [96(44.2%)] and abdominal pain [81(37.3%)]. Other important symptoms were rash, myalgia, jaundice and conjunctival congestion. Symptoms like cough, dyspnea, joint pain were seen very rarely. Table 5 shows the clinical signs associated with Scrub typhus. Eschar which is pathognomonic of Scrub typhus was seen in 68(31.3%) cases and the common sites were back, axilla, thigh and groin. Other signs like lymphadenopathy was seen in 78(35.9%), hepatomegaly in 48(22.1%) and splenomegaly in 31(14.3%) cases. Platelet count was decreased in 55(25.3%) patients. Table 6 shows the complications that occurred in Scrub typhus patients. Complications developed in 45(20.7%) Scrub typhus patients. Complications were mainly hepatic dysfunction [22(48.9%)], hepatorenal failure [8(17.7%)], ARDS [3(6.7%)], Pleural effusion [3(6.7%)] and Multiorgan dysfunction [3(6.7%)]. Other complications were two cases of meningitis, one case of meningoencephalitis, cardiomegaly, cholangitis and perinephric effusion. Complications were mainly seen in elderly adults. Out of the 217 Scrub typhus cases, 6 patients expired due to complications like MODS, renal failure, meningitis, meningoencephalitis and myocardits. Mortality rate was 2.8%. One male and five female in the age group of 50-70 years was expired.
Table 6. Complications associated with Scrub typhus.

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic dysfunction</td>
<td>22(48.9%)</td>
</tr>
<tr>
<td>Hepatorenal failure</td>
<td>8(17.7%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3(6.7%)</td>
</tr>
<tr>
<td>ARDS</td>
<td>3(6.7%)</td>
</tr>
<tr>
<td>MODS</td>
<td>3(6.7%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2(4.4%)</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>1(2.2%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1(2.2%)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>1(2.2%)</td>
</tr>
<tr>
<td>Perinephric effusion</td>
<td>1(2.2%)</td>
</tr>
</tbody>
</table>

Discussion

A hospital-based cross-sectional study was conducted among febrile patients to study the prevalence, clinical features and the complications of Scrub typhus. About 1268 patients presented with acute febrile illness over a period of one year were screened by in Biso IgM ELISA. Of these 217(17.1%) patients were positive for Scrub typhus. The prevalence of Scrub typhus varies from 0-8% to 60% in different countries (Ramayaseer et al., 2015). A study done in Christian Medical College and Hospital, Ludhiana in 2014 reported that out of 772 fever patients, 12.69% positive for Scrub typhus (Oberoi and Varghese, 2014). Another study done in Nehru Hospital of Postgraduate Institute of Medical Education and Research observed that 24% of patients presenting with unexplained febrile illness had Scrub typhus (Kumar et al., 2014). A study done in a tertiary health care institution in Goa (2012) found that 34% of fever cases were positive for IgM antibodies against O. tsutsugamushi (Kedareshwar et al., 2012). In this study, it is observed that out of the 217 Scrub typhus positive cases, there were 118 males and 99 females and adult males were mainly affected. Bhattia and Pradhan (2013), in their study found that among 204 samples were screened, 63 patients were confirmed positive among which 42 were male and 21 were female. The study by Ramyasree et al. (2015) reported that out of 39 patients, 23 were males and 16 were female. Study done by Mahajan (2014) reported that among Scrub typhus positive samples, 24% were male and 14.6% were female.

Most of the symptoms of Scrub typhus are non-specific in nature, including fever, breathlessness, nausea, headache, vomiting, and myalgia, 100% of patient presented with fever. Eschar at the site of attachment of the larval mite or chigger, is the most characteristic feature of Scrub typhus, but not seen in all patients may be due to variation in serotypes among the regions and also the eschar is usually painless and does not itch, so remains undetected. Eschar was seen in 68(31.3%) patients in this study. Varghese et al. (2013) in his study reported that eschar was found in 86(55%) patients. The presence of eschar and rash varies in different populations in different studies (Ogawa et al., 2002).

Vivekanandandan et al. (2010) reported that eschar was seen in 23 cases (46%) and the common sites were axilla, breast and groin. Multiple Organ Dysfunction Syndrome (MODS) was present in one third of patients (34%), renal impairment (91%), ARDS (8%) and meningitis (14%) were some of the important complications. In this study, hepatomegaly is seen in 48(22.1%), splenomegaly in 31(14.3%) cases. Platelet count was decreased in 55(25.3%) patients. Hepatic dysfunction, Hepatorenal failure, ARDS, Multorgan dysfunction, meningitis, meningoencephalitis were seen as complications. The study done in Manipal College of pharmaceutical sciences reported ARDS (11.5%), meningoencephalitis (8.5%), pneumonia (5.5%) as complications of Scrub typhus (Inamdar et al., 2013).

The most common complication noticed was hepatitis (80%) followed by acute respiratory distress syndrome (60%) and acute renal failure (33%) in the study of Kedareshwar et al. (2012). Tsay and Chang (1998) reported serious complications like pneumonitis (36%), acute respiratory distress syndrome (ARDS) (15%), acute renal failure (9%), myocarditis (3%) and septic shock (3%). The various complications known with this disease are jaundice, renal failure, pneumonitis, acute respiratory distress syndrome (ARDS), septic shock, myocarditis and meningo-encephalitis. Salludheen et al. (2012) reported two cases of Scrub typhus meningoencephalitis from northern Kerala. The study conducted by Singh et al. (2014) found that hepatitis (78.7%), ARDS (19.2%), thrombocytopenia (46.8%) and acute renal failure (31.9%) seen as complication and mortality occurred in 3(6.4%) patients. The complications of Scrub typhus usually develop after the 1st week of illness (Kumar et al., 2012). Six confirmed cases expired due to complications mainly hepatorenal failure, MODS, meningitis, meningoencephalitis and myocarditis and the mortality rate was 2.8%. Fatality rate was 7.8% in the study done by Varghese et al. (2013). Doxycycline (100 mg) orally twice daily was given for all patients except some pediatric cases, those were given Azithromycin. All the patients responded promptly after empirical Doxycycline therapy, with rapid resolution of symptoms in 1-3 days. Vivekanandandan et al. (2010), also reported that empirical therapy with Doxycycline may be life saving when clinical suspicion is high, even if Weil Felix test is negative and, eschar is not present. Mitrakrishnan et al. (2014) in their study reported that Azithromycin however is equally effective as Doxycycline in the treatment of Scrub typhus. They recommended that azithromycin can be used as the 1st line agent in children under the age of eight, pregnant women, in cases of suspected resistance, regions with high prevalence of strains with resistance to doxycycline, severely ill patients and patients with doxycycline intolerance.
Conclusion

*Scrub typhus* has emerged as an important cause of febrile illness. The infection manifests clinically as a non-specific febrile illness accompanied by headache, myalgia, nausea, vomiting, diarrhoea, cough or breathlessness. The vector is the larva of trombiculid mites; in which trans-ovarian transmission maintains the infection in nature. The eschar is the pathognomonic sign of *Scrub typhus* and is seen in less than 10% of cases in the Indian subcontinent. Therefore, in the absence of eschar, it is difficult to distinguish *Scrub typhus* clinically from other common acute febrile illness like typhoid, leptospirosis, malaria and dengue fever. Empirical therapy with Doxycycline may be life saving when clinical suspicion is high. There is enormous antigenic variation in *Orientia tsutsugamushi* strains and immunity to one strain does not confer immunity to another. Indirect immunofluorescence antibody assay and indirect immunoperoxidase test are the gold standard diagnostic tests for *Scrub typhus*. Doxycycline (200 mg/day) is the treatment of choice for *Scrub typhus*. Other antibiotics useful for the treatment of this infection are azithromycin, chloramphenicol, rifampicin and quinolones.

References
