

## Outbreak of Scrub Typhus in Manipur – Experience at a Tertiary Care Hospital

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### Abstract

**Aim:** To describe the clinical features, laboratory manifestations, complications in patients diagnosed with scrub typhus at a tertiary care hospital in north east India.

**Material and Methods:** All cases of acute onset fever diagnosed to have scrub typhus August 2017 to December 2018 were analysed. Cases of scrub typhus with a positive immunochromatography test were studied.

**Results:** 176 confirmed cases of scrub typhus were studied over a period of 18 months. Majority (96%) of patients are from rural background. Farmers constituted 60% of the patients. Most common symptoms were fever with headache 100 (56.8%) and due to the involvement of respiratory tract in the form of cough in 94(53%) patients followed by breathlessness in 84 (47.7%). Signs of consolidation were seen in 80 (45.5%). Central nervous system involvement in the form of altered sensorium was seen in 43 (24.4%) and seizures in 11(6.3%) patients. Eschar was seen in 23 (13%) patients. Transaminases were elevated in 153(86%) patients, serum alkaline phosphatase in 110 (62.5%) patients. Renal failure was seen in 49(27.8%) cases and respiratory failure was seen in 11 (6.2%). Eight (4.5%) patients died in our study.

**Conclusion:** Scrub typhus should be suspected in patients with rural background with fever and multi system involvement. The predominant symptoms were headache ,cough and breathlessness. Central nervous system abnormalities in the form of altered sensorium was seen in 43(24.4%). Most common laboratory abnormality noted in our patients with scrub typhus was elevated liver enzymes which were seen in 153 (86%) cases.

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### I. Introduction

Scrub typhus is caused by *Orientia tsutsugamushi* (*O.tsutsugamushi*) an obligatory intra-cellular gram negative bacterium. It is transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*.<sup>1</sup> Scrub typhus, if undiagnosed or diagnosed late, or untreated, may prove fatal. The clinical manifestations of this disease range from sub-clinical disease to organ failure.<sup>2,3</sup> Fever is the most common feature of scrub typhus and due to lack of awareness among clinicians the condition is labelled as “fever of unknown origin”.<sup>4</sup> Scrub typhus has protean manifestations which can mimic conditions like pneumonia, meningoencephalitis, acute hepatitis, acute renal failure, loose motions and occasionally joint pains. Scrub typhus may occasionally present as fever of unknown origin and due to lack of awareness of the disease, clinicians spend a lot of time and resources during the work up. The clinical course of the disease and the prognosis vary depending on the character of the endemic strain.<sup>5</sup> Lack of access to specific laboratory tests is another problem in developing countries like India for the under diagnosis of several infectious diseases including scrub typhus. Recent reports from several parts of India, including north east India, indicate that there is a resurgence of scrub typhus.<sup>2,6,7</sup> There are very few publications on scrub typhus from the state of Manipur.<sup>8,9</sup> We present our experience on clinical and laboratory features of patients with scrub typhus.

### II. Material and Methods

This is a retrospective observational study of patients with scrub typhus who were admitted between August 2017 and December 2018 in the Medicine department of JNIMS, Porompat. Data of clinical and laboratory features of patients aged more than 12 years, with fever, and confirmed diagnosis of scrub typhus was collected and analysed. Scrub typhus cases confirmed by a positive immunochromatography test were included in the study. Patients with other established causes of fever were excluded from this study.

### III. Results

Study population was recruited after the start of the monsoon season in 2017 August to the end of October 2018. Patients with scrub typhus were identified on the basis of clinical features and serology. Data of 176 patients with scrub typhus were recorded from the case records and were analysed. Most of the cases are seen in months of monsoon and post monsoon period i.e., August, September and October. The baseline characteristics of the study patients are shown in Table 1. Mean age of the study population is 41 years ( $\pm 16$ ). There were 105 (59.7%) males and 71(40.3%) females in our study. Most of the patients are from rural background with history of working in open fields. One hundred and seventy (96.6%) patients are from the rural part of Manipur and the rest of the patients, i.e. 6 (3.4%) patients visited rural parts of the state in the recent past.

**Table 1:** Showing baseline characteristics of the patients.

Characteristics of the patients	No. of patients (%)
Male	105 (59.7%)
Female	71 (40.3%)
Rural background	170 (96.6%)
Urban	6(3.4%)
Farmers	104 (59.1%)
Housewife	36(20.5%)
Others	36 (20.5%)

The clinical features of the patients are shown in Table 2. All patients presented with fever and the average duration of fever was 11.8 days (range 2 to 30 days). Majority of patients i.e. 73(41.5%) patients presented with fever of 7-14 days duration. Forty (22.7%) patients presented to us as prolonged pyrexia as fever was persisting beyond 14 days. Most common symptom was headache (56.8%),and cough (53.4%). The next most common symptom was breathlessness, which was present in 84 (47.7%) patients. Loose motions were seen in 28(15.9%) patients. Seizures were present in 11(6.3%) patients and one patient presented with status epilepticus. Joint pains were seen in 5(2.8%) patients.

**Table 2:** showing the symptoms and signs

Symptoms	No. of patients (%)
Fever duration < 7 days	63 (35.8%)
Fever duration 7-14 days	73(41.5%)
Fever duration > 14 days	40 (22.7%)
Cough	94 (53.4%)
Breathlessness	84(47.7%)
Jaundice	40(22.7%)
Diarrhoea	28(15.9%)
Seizures	11(6.3%)
Status epilepticus	1(0.5%)
Joint pains	5(2.8%)
Hepatosplenomegaly	51(28.9%)
Altered mental status	43(24.4%)
Eschar	23(13.1%)
Creptitations in lungs	80(45.5%)
Headache	100(56.8%)

Maculopapular rash was seen in 10 (5.7%) patients. Eschar was seen in 23 (13.1%) patients in our series. The most common abnormality on examination seen was lung involvement in the form of creptitations in 80(45.5%) patients. Twenty-three (13.1%) patients had altered mental status. The other signs of organ involvement observed were hepatosplenomegaly in 51 (28.9%) patients.

Laboratory features are shown in Table 3. Mean haemoglobin was 11.1g/dl ( $\pm$  SD $\pm$ 2.3). Leucopenia (TLC < 4000/cmm) was seen in 18(10.2%) patients. Leucocytosis was seen in 42(23.9%) patients. Thrombocytopenia (platelet count < 100000/cmm) was seen in 53(30.1%) patients. Elevation of serum creatinine i.e. 1.6 mg/dl was seen in 49(27.8%) patients. Elevation in serum aspartate transaminase (AST) was noted in 153(86.9%) and serum alanine transaminase (ALT) in 136 (77.3%) patients. Cardiac conduction abnormalities in the form of relative bradycardia (corresponding to temperature record) were seen on electrocardiogram in 6 (3.4%) patients. Dialysis was needed in 5 (2.8%) patients. Ventilatory support was needed in 8(4.5%) patients.

**Table 3:** showing the laboratory abnormalities

Investigations	No. of patients
Mean Haemoglobin	11.1
Leucopenia	18(10.2%)
leucocytosis	42(23.9%)
Platelet count < 1 lakh	53(30.1%)
Elevated SGOT	153(86.9%)
Elevated SGPT	136(77.3%)
Elevated serum creatinine	49(27.8%)
Elevated serum ALP	110(62.5%)
Infiltrating on chest x-ray	46(26.1%)
Bradycardia	6(3.4%)

Average duration of hospital stay was 7.2 days (SD:  $\pm$  3.95). Duration of hospital stay of less than 7 days was noted in 121(68.8%) patients. Forty six (26.1%) patients had a hospital stay of 8-14 days. Nine (5.1%) patients stayed for more than 14 days in the hospital. All patients were treated with doxycycline orally and supportive care. Out of 176 patients 168 (95.5%) recovered and eight (4.5%) patients died. One (0.5%) patient left against medical advice.

#### IV. Discussion

It is important to rapidly delineate the cause of fever in regions where several infections like dengue fever, malaria, scrub typhus, and community-acquired pneumonia are common. Finding the exact aetiology is important as treatment is different for each disease and unnecessary use of antimicrobial agents can be avoided. In India, epidemics of scrub typhus have been reported from north east and south India<sup>5-7,10</sup> We have observed a sudden outbreak of scrub typhus from this part of the country.

*O.tutsugamushi*, an obligate intracellular bacterium transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*.<sup>1</sup> These larval mites usually feed on the wild rats of the subgenus *Rattus*. The organism is maintained by transovarian transmission in mites. There are several serotypes of *O.tutsugamushi* and infections with one-serotype gives only transient cross immunity to another.<sup>7</sup> Man is accidentally infected when he encroaches the mite-infested areas with secondary scrub growth, which grows after the clearance of primary forest. The basic pathologic changes are focal vasculitis and perivasculitis of the small blood vessels in the involved organs, arising from multiplication of the organisms in the endothelial cells lining the small blood vessels.<sup>11,12-14</sup>

In the present study most of the cases were seen during the months of July to November. Scrub vegetation, optimum amount of monthly rainfall, and soil bound moisture are important factors responsible for disease transmission.<sup>15</sup> Consequently, an increase in incidence of cases is seen in the rainy season.<sup>16</sup> One more reason for increased incidence during the months of August to October is that, farmers are involved in the harvesting activity in the fields, where they are exposed to the bites of larval mites.<sup>10</sup> However, there are descriptions of scrub typhus outbreaks in cooler seasons also.<sup>16</sup> This is possibly due to the growth of secondary scrub vegetation, which is the habitat for trombiculid mites (mite islands in the immediate post monsoon period i.e. September to early months of the next year).<sup>1</sup>

As described in literature the disease is common in farmers, persons rearing domestic animals and those living close to bushes and woodpiles.<sup>17</sup> Farm work and related activities were noted in 60% in our study and it is comparable to other studies in the literature.<sup>18,19</sup> Almost all the patients were from rural background in our study. The mean age of our patients is 41 years and majority were men. Age and sex can occasionally influence the incidence of scrub typhus mainly due to the exposure to outdoor activities in the younger adults. Whether occupational or recreational, more common in 21-50 years and those involved in outdoor activities.<sup>20</sup>

The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash.<sup>1,21</sup> An eschar at the wound site is the single most useful diagnostic clue and it is very important to perform a thorough physical examination to look for eschar and signs to exclude other causes of fever. Though eschar was pathognomonic of scrub typhus, it was noted only in 23 (13.1%) of our patients. Similar number of eschars reported in other Indian studies by Mathai et al (2003) and Vivekananda et al (2010). The reason for the less number of eschar in Indian studies may be due to the high skin colour of the population and due to variation of serotypes among different regions.<sup>6</sup> Maculopapular rash was seen in 10 (5.7%) patients in our series and is comparable to other Indian studies.<sup>7,15</sup>

Most of our patients with scrub typhus presented with non-specific symptoms of gastrointestinal and respiratory tract involvement mimicking viral fever. One of the clinical differentiating features in scrub typhus from other viral illnesses like dengue is the duration of fever. Average duration of fever in our study group was 11.8 days (ranging from 2 to 30 days). Forty (22.7%) patients presented with prolonged pyrexia i.e., fever more than 2 weeks duration.

Scrub typhus involves multiple organs including the lung, heart, central nervous system (CNS), and is characterised by focal vasculitis or perivasculitis. Such microangiopathies may also involve the kidney (acute renal failure), gastrointestinal tract (gastrointestinal bleeding), liver (hepatic dysfunction and hepatomegaly), spleen (splenomegaly), and lymph node (lymphadenopathy).<sup>12</sup>

Respiratory tract involvement is a common manifestation of scrub typhus and clinicians need to differentiate it from community-acquired pneumonia caused by the usual organisms like streptococcus species. Cough and breathlessness were present in 94 (53.4%) and 84 (47.7%) patients respectively in our series. Eighty (45.5%) patients had signs of consolidation on clinical examination. Respiratory failure is a common complication of scrub typhus and was reported in 11% of cases in one large series.<sup>22</sup>

In our series, 11(6%) patients developed respiratory failure out of which 8 patients required ventilator support and 3 patients needed high flow oxygen support. Chest radiograph abnormalities in the form of reticulonodular opacities, air space consolidation, peribronchial infiltration, pulmonary congestion, pulmonary oedema, acute respiratory distress syndrome (ARDS) and pleural effusion were known to occur in scrub typhus.<sup>22,23</sup>

Gastrointestinal system symptoms in the form of vomitings and loose motions are common presenting features of scrub typhus. Loose stools were seen in 28(15.9%) patients in our series. Clinician should suspect scrub typhus in a case of fever and diarrhoea if accompanied by symptoms of respiratory or central nervous system symptoms in an endemic area and it helps in differentiating from infective diarrhoea. Hepatosplenomegaly was seen in 51(28.9%) patients of our series. Among the gastrointestinal manifestations, elevated hepatic transaminases are a striking feature in scrub typhus that physicians need to pay attention in an endemic area. We have observed an elevation in transaminases in which ALT was found to be more than AST similar to the reports found in literature.<sup>4</sup> Apart from transaminases, elevated serum alkaline phosphatase and serum bilirubin were seen in 110 (62.5%) and 68(38.6%) patients respectively in our study in comparison to other studies.<sup>7,15,24</sup>

Renal failure was the next complication after hepatitis in our series. Elevation of serum creatinine > 1.6 mg/dl was seen in 49(27.8%) patients in which 5(2.8%) patients required dialysis. Renal failure was seen in 13-37%<sup>7,15</sup> from two different studies from India.

Scrub typhus, as the name suggests is characterised by fever with altered sensorium. In our study, the most common symptom is fever associated with headache which occurs in 56.8% of patients. CNS involvement ranges from aseptic meningitis to frank meningoencephalitis.<sup>25</sup> The pathologic changes in the brain are predominantly vascular in nature and actual tissue destruction is rare and they are potentially reversible despite widespread lesions.<sup>22</sup> As reported in other series in literature, 33 (18.8%) of our patients had drowsiness on examination during hospital stay. Seizures were present in 11(6.3%) and one patient presented with status epilepticus. All patients including the one with status epilepticus responded to treatment with doxycycline.

The existence of myocarditis in scrub typhus is easily ignored, because the symptoms of myocardial involvement are usually subclinical and sometimes may lead to heart failure also.<sup>26</sup> Cardiac conduction abnormalities in the form of bradycardia were seen on electrocardiogram in 6 (3.4%) patients, and we observed bradycardia on ECG in 6(3.4%) of our patients. Other febrile illnesses with relative bradycardia include dengue fever, brucellosis, chlamydiosis, legionellosis and enteric fever.<sup>27</sup>

Another feature noted in our series was arthralgia in 8(4.5%) which was rarely reported in literature and only one study from India by Patil et al reported in 27% patients in their study from Karnataka.<sup>28</sup> Arthralgias are commonly described in other febrile illnesses like dengue fever and chikungunya fever and need to be differentiated from each other as treatment is different for scrub typhus.

Complete blood counts and peripheral smear examination initially help in differentiating aetiology of fever, which is important in developing countries like India where there are limited resources. Among the laboratory abnormalities, most common haematological abnormality noted was thrombocytopenia in 53(30.1%) patients followed by leucocytosis in our series. Similar observation was made by other studies. This helps in clinching the diagnosis to scrub typhus. In complicated falciparum malaria there will be anaemia, leucopenia usually and thrombocytopenia occasionally. In dengue fever there will be haemoconcentration, leucopenia and thrombocytopenia.

Antibiotics of the tetracycline class (doxycycline in particular) have a high degree of efficacy and low toxicity in treating rickettsial infections, even in children and pregnant women. The treatment of choice for scrub typhus infection is doxycycline 100 mg per dose administered twice daily (orally or intravenously) for adults or 2.2 mg per Kg for children less than 45.5 Kg.<sup>33</sup> This treatment should be started empirically as soon as diagnosis is suspected. The optimal duration of treatment has not been established, but current recommendation suggests at least 3-7 days for life threatening cases to a maximum of 15 days for severe or complicated disease. Alternatively chloramphenicol (500 mg 4 times a day orally for 7 days in adults or 150 mg per kg per day for 5 days in children) in endemic areas has been proven effective in treating scrub typhus and preventing relapse.<sup>33</sup> Rifampicin or azithromycin are effective in doxycycline resistant strains of scrub typhus.

Outcome of the patients admitted with scrub typhus was studied. All our patients are treated with doxycycline and supportive care. Doxycycline was given for 7 days in mild disease and 14 days for patients with multiorgan disease. Out of 176 patients 168 (95.5%) recovered, one (0.5%) patient left against medical advice and eight (4.5%) patients died. The main cause of death is ARDS and the mortality in our study is comparable to other Indian studies.<sup>7,16,30</sup> and a large study from Taiwan reported less (2-3%) mortality. The low mortality in Taiwan may be due to the endemicity of the disease and familiarity of the disease among the clinicians. The deaths in our series are possibly due to delayed diagnosis, late presentation and multiorgan dysfunction.

## V. Conclusion

Scrub typhus clinically mimics infections like dengue viral infection, leptospirosis, malaria, pneumonia as all of them may be associated with sudden onset fever, mild hepatitis and thrombocytopenia. Associated headache, respiratory involvement, gastrointestinal symptoms, altered sensorium and hepatitis should prompt physicians for a diagnosis of scrub typhus. Majority of our patients with scrub typhus are from rural parts of Manipur. Though eschar is pathognomonic of the disease, it was noted in 23 (13.1%) patients and its absence does not rule out scrub typhus. Fever with headache are the most predominant symptoms while transaminases are the most predominant laboratory abnormality in our series. We conclude to say that in rural Manipur patients who present with fever, headache, respiratory symptoms and hepatitis scrub typhus should be suspected. As delay in treatment may lead to complications and higher mortality, empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and facilities for diagnosis are not available.

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