



ORIGINAL RESEARCH PAPER

General Medicine

SCRUB TYPHUS AMONG INPATIENTS IN A TERTIARY CARE HOSPITAL IN SOUTHERN RAJASTHAN – A CLINICO-EPIDEMIOLOGICAL STUDY

KEY WORDS: Scrub Typhus, Eschar, Mods, Ards.

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ABSTRACT

BACKGROUND : Scrub typhus or tsutsugamushi disease is a febrile illness caused by Orientia tsutsugamushi. Increased incidence of this fever had been reported in recent past. The present study was conducted to find out the clinical features, complications, response to treatment and outcome of patients suffering from scrub typhus in a tertiary health care institute in south-east Rajasthan, India.

METHODS: A hospital based prospective observational study of patients of acute febrile illness performed at tertiary health care institute in south-east Rajasthan. patients of acute febrile illness of more than 14 years of age, admitted in medicine department during November 2018 to October 2019, with IgM ELISA positive for Scrub Typhus were enrolled in the study as study participants. All such patients underwent detailed clinical examination and investigation.

RESULTS : A total of 134 patients were diagnosed with scrub typhus, with females more than males and most common age group was 31 to 40 years(29.9%). Most common presenting symptom was fever (100%) followed by Headache(80.59%) and Dry Cough(66.42%) while Rash was present in only 14.18%. ESCHAR which is pathognomic of scrub typhus was found in 46.27% patients. Most common complication was pneumonia (39.6%) followed by hepatitis (35.8%),MODS (29%), ARDS(23.1%), septic shock (17.2%), acute kidney injury(9%) and all of them were significantly associated with mortality (p<0.05). Mortality was observed in 6.7% of cases.

CONCLUSION : Scrub typhus is an important cause of acute febrile illness with multisystem involvement in south eastern belt of Rajasthan. A high index of suspicion is needed in patients presenting with fever especially during monsoon and post monsoon season. In resource limited settings and pending laboratory confirmation we should implement a 'suspect and treat' strategy and initiate prompt treatment with Doxycycline or Azithromycin, to prevent serious morbidity and fatality in this potentially treatable and curable disease.

INTRODUCTION :

Rickettsial diseases are considered as some of the most covert emerging and re-emerging diseases and are being increasingly recognized. Among these, Scrub typhus is the commonest occurring rickettsial infection in India. Scrub typhus or tsutsugamushi disease, is an acute febrile illness in humans caused by infection with Orientia tsutsugamushi following a bite of an infected mite vector of the genus Leptotrombidium. The World Health Organization has dubbed scrub typhus one of the world's most under-diagnosed /under-reported diseases that often requires hospitalization^[1] highlighting the necessity for a better understanding of the vectors, outbreaks, and pathogenesis associated with this potentially fatal organism that has been linked to human cases/outbreaks both within and beyond its previously recognized region of endemicity. Scrub typhus is endemic in the Asia-Pacific region, extending from Afghanistan to China, Korea, the islands of the western Pacific and Indian Oceans, and northern Australia^[2]. This endemic region is often referred to as the tsutsugamushi triangle. Recent reports from several parts of India indicate that there has been a resurgence of the disease^[3]. The agent Orientia tsutsugamushi which is an obligate intracellular bacteria that is transmitted by larval trombiculid mite, which is the reservoir of the agent and the only life stage that feeds on a vertebrate host. The clinical syndrome classically consists of fever, rash and eschar and requires laboratory confirmation of diagnosis^[4]. It should be considered as a differential diagnosis in patients with acute febrile illness including those with thrombocytopenia, renal impairment, LFT abnormality, altered sensorium, pneumonitis or ARDS. A thorough search for eschar, particularly in hidden areas is useful for diagnosis. Eschar may not be present in a large number of cases^[5].

Clinical symptoms of scrub typhus range from sub-clinical disease to multi-organ failure. The complications of scrub typhus usually develop after the first week of illness. Jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis and meningo-encephalitis are various complications known with this disease^[5]. The drug of choice for the treatment of scrub typhus is Doxycycline 200mg twice daily PO for 10 days.^[6] In children and pregnant women Azithromycin 500mg once daily for 5 days is preferred. Rifampicin is an alternative drug but is not to be given alone to avoid the development of drug resistance.

NEED FOR THE STUDY :

Scrub typhus may cause mild symptoms, serious complications, or even death. Mortality rates in untreated patients range from 0% to 30% and tend to vary with different geographical regions. The goal of this Prospective study was to provide a detailed panel of clinical aspects of this disease based on a large patient population, thus helping to create a better clinical and laboratory profile of this re-emerging disease for clinicians to work with.

MATERIAL AND METHODS :

We did a hospital based prospective observational study in the department of General Medicine.

STUDY DESIGN :

This was a prospective observational study in which patients were being included prospectively, with a sample size of 134.

STUDY DURATION :

This study duration was 12 months – November 2018 to October 2019.

INCLUSION CRITERIA :

All the adult patients with acute febrile illness with Scrub typhus IgM ELISA positive, that consented to participate in the study were recruited.

EXCLUSION CRITERIA:

Acute febrile illness patients with IgM ELISA negative for Scrub typhus. Patients with co-infection with dengue or malaria. Patient having co-morbid condition like chronic renal failure, chronic liver disease, patient with known neoplastic disease etc. Patients who were unwilling to consent, or refused to having their blood drawn or used for research purpose.

After admission to the internal medicine ward, we took informed consent from each participant prior to examination. The residents (under supervision of faculty) were evaluating all the patients with acute febrile illness by reviewing history and focused physical examination. We advised IgM ELISA (Scrub typhus Detect™ IGM ELISA system manufa ct ured by In Bios International, Inc., USA) for scrub typhus for all acute febrile illness patients without definitive source of infection (pulmonary tuberculosis, urinary tract infection, pneumonia, skin or soft tissue infection, malaria, dengue etc.). Patients with IgM ELISA positive who meet the inclusion and exclusion criteria were recruited for the study. In addition to detailed history and physical examination, we evaluated scrub typhus patients for severity and complications by other investigations as per protocol.

For the diagnosis of associated complication and ease of comparison same standard definitions were used as in other study on scrub typhus^[13].

- Leukocytosis : as total leukocyte count >11000 cells/ml.
- Leukopenia : as total leukocyte count <4000cells/ml.
- Thrombocytopenia: as platelet count <150000 cells/mL.
- Hypoalbuminemia : as serum albumin <3.5 g/dl.
- Pneumonia: radiologic evidence of opacities.
- Multiple-organ dysfunction syndrome (MODS): Dysfu nction of more than one organ, requiring intervention to maintain homeoestasis.
- Acute kidney injury: A rise in serum creatinine of more than 1.6 mg/dl or urine output less than 400 ml/24 hrs failing to improve after adequate rehydration.
- Acute respiratory distress syndrome (ARDS): Bilateral alveolar or interstitial infiltrates on chest radiograph and PaO2/FiO2 less than or equal to 200mmHg.
- Hepatitis: Rise in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of more than 2.5 times the upper normal limit (i.e., >100 IU/l); and/or elevation of serum bilirubin >2.5mg/dl.
- Meningitis: Altered sensorium with feature of meningeal irritation like neck rigidity, positive Kernig's sign with elevated protein and/or polymorphic leucocytosis on CSF analysis.
- Shock: Systolic blood pressure of < 90 mm Hg for at least 1 h despite adequate fluid resuscitation was labelled as

shock.

All patients diagnosed to have scrub typhus or those with strong clinical suspicion of scrub typhus were treated with doxycycline in the dose of 100 mg twice daily PO for 10 days unless it is contraindicated like pregnancy. In cases where doxycycline was not used azithromycin in a dose of 500 mg once daily for 5 days given. As per indication other supportive measure were given like haemodialysis, mechanical ventilation, blood transfusion, ionotropic agent etc.

RESULTS

AGE & GENDER :

Table 1 depicts that highest number of patients were seen in the age group of 31-40 years is 40 (29.9%) followed by 51-60 years is 23 (17.2%), 21-30 years is 20 (14.9%). Study participants constitute 60(44.8%) males and 74(55.2%) females. Mean age of patients was 40.78±15.9 years. Mean age in males was 40.58±16.3 years while in females 40.93±15.7 years.

Table 1 : Distribution of Patients according to AGE AND GENDER.

| Age in yr | Patient of scrub typhus | | |
|-----------|-------------------------|------------|------------|
| | Male (%) | Female (%) | TOTAL (%) |
| 11 - 20 | 9 (15) | 10 (13.5) | 19 (14.2) |
| 21 - 30 | 10 (16.7) | 10 (13.5) | 20 (14.9) |
| 31 - 40 | 15 (25) | 25 (33.8) | 40 (29.9) |
| 41 - 50 | 8 (13.3) | 8 (10.8) | 16 (11.9) |
| 51 - 60 | 12 (20) | 11 (14.8) | 23 (17.2) |
| 61 - 70 | 5 (8.3) | 9 (12.2) | 14 (10.4) |
| >71 | 1 (1.7) | 1 (1.4) | 2 (1.5) |
| Total | 60 (44.8) | 74 (55.2) | 134 (100) |
| | 40.58±16.3 | 40.93±15.7 | 40.78±15.9 |

SEASONAL VARIATION :

Incidence of scrub typhus was more during rainy season. In our study maximum incidence was in October month 62 (46.3%) patients, followed by September 50 (37.3%) and 20 (14.9%) in August.

SIGN & SYMPTOMS :

Fever was the main presenting symptom, found in almost all 134(100%) patients, followed by headache 108 (80.59%), myalgia 86(64.18%), cough 89(66.42%), nausea/vomiting 71(52.98%). Majority of patients 96(71.65%) presented with high grade fever(>100°F) associated with chills and rigor. Maximum patients 85(63.4%) present with fever of 8 to 21 days. Mean duration of fever was 10.57±5.64 days in all patients. Eschar which is characteristic of scrub typhus was found in 62 (46.27%) patients. Highest number of eschar were found in inguinal region 24(38.8%), followed by axillary area 15(24.2%), on the trunk 12(19.4%), inframammary region 5(8%), and penile area 4(6.4%). Majority of patients had hepatosplenomegaly 87(64.93%) followed by lymphad eno pathy 50(37.31%).(Table 2)

Table 2 : Clinical Symptoms & Signs in patients of Scrub Typhus

| Symptoms | Number of Patients (n=134) | Signs | Number of Patients (n=134) |
|----------------------------------|----------------------------|---------------------------|----------------------------|
| Fever | 134(100%) | Eschar | 62(46.27%) |
| Headache | 108(80.59%) | Lymphadenopathy | 50(37.31%) |
| Myalgia | 86(64.18%) | Hepatosplenomegaly | 87(64.93%) |
| Cough | 89(66.42%) | Hypotension | 24(17.91%) |
| Jaundice | 35(26.12%) | Crackles/Rhonchi | 40(29.85%) |
| Nausea/ Vomiting | 71(52.98%) | Others | 24(17.91%) |
| Pain Abdomen | 34(24.37%) | | |
| Diarrhea | 4(2.98%) | | |
| Confusion/ altered mental status | 36(26.86%) | | |
| Rash | 19(14.18%) | | |

| | | | |
|---------------------------|------------|--|--|
| Generalized body swelling | 24(17.91%) | | |
| Others | 17(12.68%) | | |

Table show laboratory profile of scrub typhus patients that high wbc count, bilirubin, AST level, blood urea & Serum creatinine level while low platelet count, protein, albumin and serum calcium level were statistically significant in term of poor outcome. (Table 3)

Table 3 : LABORATORY FINDING IN PATIENTS WITH SCRUB TYPHUS

| | Survived(n=125) | Death(n=9) | P-Value |
|-----------------------------|---------------------|--------------------|--------------|
| Hematological | | | |
| WBC (per µl) | 8943.76±3941.14 | 13217.78±9075.2 | 0.006 |
| HEMATOCRIT(%) | 32.12±7.32 | 35.28±4.62 | 0.205 |
| PLATELET (per µl) | 158274.40±52747.229 | 38088.89±26232.063 | 0.001 |
| Liver Function | | | |
| BILIRUBIN(TOTAL)(mg/dl) | 1.84±0.70 | 4.3±1.8 | 0.001 |
| BILIRUBIN(Direct) (mg/dl) | 0.92±.58 | 2.69±1.19 | 0.014 |
| BILIRUBIN(Indirect) (mg/dl) | 0.99±0.66 | 1.61±.66 | 0.002 |
| ALT(IU/L) | 106.35±70.39 | 174.89±123.31 | 0.157 |
| AST(IU/L) | 166.71±108.40 | 427.78±285.98 | 0.035 |
| PROTEIN (g/dl) | 6.06±1.015 | 5.16±0.61 | 0.016 |
| ALBUMIN (g/dl) | 2.84±0.66 | 2.23±0.29 | 0.007 |
| GLOBULIN (g/dl) | 3.19±0.62 | 2.93±0.51 | 0.215 |
| Renal Function | | | |
| B. UREA(mg/dl) | 37.83±28.58 | 109.22±56.83 | .001 |
| S. CREATININE | 0.92±0.83 | 2.19±1.23 | .001 |
| Electrolyte profile | | | |
| Na(mmo/L) | 135.48±5.990 | 136.78±3.383 | 0.523 |
| K(mmo/L) | 3.922±.6278 | 3.811±.6528 | 0.612 |
| Ca(mmo/L) | 8.7234±.70860 | 7.9889±.94133 | 0.004 |
| CK-MB(IU/L) | 34.67±32.19 | 53.57±15.08 | 0.131 |

Among the complication most common was pneumonia(39.55%) followed by hepatitis(35.82%). Complication of scrub typhus like pneumonia, hepatitis, septic shock, acute kidney injury, ARDS and MODS were statistically significant in terms of poor outcome. (Table 4)

Table 4 : COMPLICATION OF SCRUB TYPHUS AND THEIR SEVERITY

| COMPLICATION | TOTAL(n=134) | Survived(n=125) | Death(n=9) | P-VALUE |
|---------------------|--------------|-----------------|------------|---------------|
| PNEUMONIA | 53(39.55%) | 46 | 7 | 0.029 |
| HEPATITIS | 48(35.82%) | 40 | 8 | 0.001 |
| SEPTIC SHOCK | 23(17.16%) | 15 | 8 | 0.0001 |
| Acute Kidney Injury | 12(8.9%) | 7 | 5 | 0.001 |
| MENINGITIS | 10(7.4%) | 8 | 2 | 0.136 |
| ARDS | 31(23.12%) | 25 | 6 | 0.005 |
| MODS | 29(21.64%) | 22 | 7 | 0.001 |

DISCUSSION :

Scrub typhus is a well known mite borne disease which is also prevalent in Rajasthan state. The state had observed many outbreak of scrub typhus in recent past. Most of the cases were seen in monsoon and post monsoon months. Scrub typhus affects about 1 million people every year worldwide. Scrub typhus presents as an acute febrile illness with non-specific sign and symptoms many times. It is a important cause of multi-organ dysfunction and admission in ICUs among patientst with acute febrile illness. Early diagnosis and treatment can prove to be lifesaving in such patients.

In our study, out of 134, males were 60(44.8%) and females were 74(55.2%) .Majority of patients were in the age group of 31 to 40 years(29.9%) . This trend was probably because this age group particularly females were main workers in agricultural field in this region. In our study majority of patients were admitted in post monsoon season in months of September & October (83.6%) . Similar results were observed in a study of Philomena J et al^[7] with most common age group affected belonged to third decade with female preponderance. In our study most of the patients were from rural area(91.4%) while majority of the patients were engaged in agricultural work(56.71%) and animal husbandry(67.91%).

(100%) followed by Headache(80.59%) and Dry Cough (66.42%) while Rash was present in only 14.18%. duration of fever was 8-14 days in 38.8% followed by 15 – 21 days in 24.6%. Majority of patients had hepatosplenomegaly (64.93%) while ESCHAR which is pathognomic of scrub typhus was found in 46.27% patients similar to a study Philomena J et al^[7] reported 45%. Among eschar positive patients most common site was inguinal area (38.8%) followed by trunk (19.4%).

Total 56% patients had platelet count below <150000/ l while 8.2% patients had severe thrombocytopenia(<20000/ l). While 29.1% patients had leucocytosis while 6.7% patients had leucocytopenia. Our study strongly favors association between leucocytosis and thrombocytopenia with poor outcome of scrub typhus. Similar result were obtained in a study by Pamornsri sriwongpan et al^[8] (2013) reported that high mean WBC count and low mean platelet count were associated with increased mortality in scrub typhus.

In our study out of 134 patients 125 discharged and 9 died(mortality 6.7%). Patients admitted with duration of fever more than 15 days had higher mortality 88.9%. While presence of eschar and treatment taken prior to admission had no impact on outcome

In our study most common presenting symptom was fever

Hepatitis is common complication of scrub typhus which affects liver function test. High bilirubin, raised AST and low serum protein specially albumin were indicator of poor outcome as observed in a study by Pamornsri sriwongpan et al^[8]. Scrub typhus also causes acute kidney injury which reflected by elevated renal function test. Renal function test including serum creatinine and blood urea level were significantly raised in death group. Serum electrolytes and Cardiac specific creatinine kinase levels correlation was not found statistically significant except serum calcium level which was significantly decreased among deceased.

In our study most common complication was pneumonia (39.8%) followed by hepatitis (35.8%), septic shock (17.2%), acute kidney injury(9%) and all of them were significantly

associated with mortality(p<0.05). Acute respiratory distress syndrome was present in 23.1% patients most of them needed critical care and ventilator support. Patients with Acute respiratory distress syndrome had higher mortality rate(p=0.005). Multiple organ dysfunction was found in 29% patients of scrub typhus with a higher mortality rate(p=0.001) Doxycycline is still drug of choice and effective in scrub typhus. There was significant clinical improvement within in 2 to 3 days. Combination of doxycycline and azithromycin was not proven superior to monotherapy. But combination was mainly given to complicated cases and severe patients. iv azithromycin given to patients who were unable to take oral drugs. Along with specific treatment like beta lactam agents were given in patients of bilateral pneumonia and ARDS.

Complications of scrub typhus : Comparison of recent studies from india

| Study | James Philomena et al ^[7] | S.P. Singh et al ^[9] | Sharma et al ^[10] | Anurag Bhargava et al ^[11] | Varghese et al ^[12] | Rishi et al (present study) |
|-------------------|--------------------------------------|---------------------------------|------------------------------|---------------------------------------|--------------------------------|-----------------------------|
| Year | 2015-2016 | 2012-2013 | 2013-2014 | 2012-2013 | 2005-2010 | 2018-2019 |
| No. Of patients | 99 | 47 | 228 | 284 | 623 | 134 |
| Study Duration | 12 months | 12 months | 18 months | 15 months | 60 months | 12 months |
| Design | Retrospecctive | Prospective | Prospective | Prospective | Retrospecctive | Prospective |
| ARDS | 11% | 19.2% | 25% | 16.2% | 33.7% | 23.1% |
| MODS | 7% | - | 20% | 16.7% | 34% | 21.6% |
| Septic Shock | - | 6% | 27% | 10.2% | 23.1% | 17.2% |
| AKI | 22% | 31.9% | 32% | 48% | 17.9% | 9% |
| Eschar | 46% | - | 14% | 17.3% | 43.5% | 62% |
| Thrombo-cytopenia | 56% | 46.8% | 90% | 80.9% | 79% | 56% |
| Acute hepatitis | 36% | 44.7% | 61% | 48% | 34% | 35.8% |
| Mortality | 6% | 6.4% | 13.6% | 8.4% | 8.9% | 6.7% |

CONCLUSION :

Scrub typhus is an important cause of acute febrile illness with multisystem involvement in south eastern belt of Rajasthan. A high index of suspicion is needed in patients presenting with fever especially during monsoon and post monsoon season. Fever, headache, myalgia, rash with high WBC, low platelet and raised liver and renal function test are usual features. Early presentation of disease with duration of fever <12 days had a better prognosis when compared with a fever duration of >15days. Though eschar is pathognomic of the disease, it may not be seen, and its absence does not rule out scrub typhus. Multiorgan dysfunction, respiratory dysfunction, hepatic dysfunction, acute kidney injury and shock are the life- threatening complications that lead to higher case fatality rates. In resource limited settings and pending laboratory confirmation we should implement a 'suspect and treat' strategy and initiate prompt treatment with Doxycycline or Azithromycin, to prevent serious morbidity and fatality in this potentially treatable and curable disease. More widespread access to medical care, coupled with the increased use of affordable and accurate rapid test, is required to improve diagnosis and treatment of this easily treatable disease.

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