

Original Research Article

Clinical spectrum and complications of scrub typhus: a single-centre, pilot observation from central India

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ABSTRACT

Background: Scrub typhus is known from various parts of India. However, reports from central India are lacking. We performed pilot observation of confirmed scrub typhus cases from a single, tertiary care centre from central India.

Methods: A retrospective analysis of 16 IgM ELISA confirmed scrub typhus cases was done. Clinical features, signs, laboratory parameters and complications were identified. Age (<40 Versus >40 years) and gender (male versus female) specific comparisons were performed. Data were analysed descriptively with appropriate statistical tests.

Results: Diagnosed cases of scrub typhus were frequent in patients aged below 40 years (68.8) and in females (81.2%). Fever (100%), nausea±vomiting (68.8%) and headache (56.2%) were common symptoms. Rash was reported in a single case whereas characteristic eschar of scrub typhus was not observed in any patient. Mean hospital stay duration did not vary either by gender or by age-groups. Laboratory abnormalities did not show any significant deviation by gender or age analysis except mean haemoglobin being lower in females than males (10.1±1.4 Vs 12.3±1.1, p<0.05). Among various complications, anaemia (56.2%), thrombocytopenia (56.2%), elevated liver enzymes (37.5%) and pleural effusion (37.5%) were frequent. Overall, the number of complications were more in females (88.2%) and younger age (73.5%) groups. No deaths were seen in our set-up.

Conclusions: Our pilot observation suggests scrub typhus is common in females and in younger age groups. These findings need further exploration in a large, prospective, trial in confirmed cases of scrub typhus.

Keywords: Age-specific, Clinical symptoms, Complications *Scrub typhus*, Gender-specific, *Orientia tsutsugamushi*

INTRODUCTION

Infections associated pyrexia in India is commonly seen with malaria, leptospirosis, dengue, enteric fever, viral and bacterial infections. However, a common endemic disease called as *Scrub Typhus* that is caused by the rickettsia *Orientia tsutsugamushi* remains hugely underdiagnosed and underreported.^{1,2} A strong surveillance is necessary as fatality is higher in untreated patients.³ Scrub typhus has been identified and reported from various parts of India.⁴⁻⁷ However, there are scant

reports from Central India region. Further, scrub typhus has been reported in all ages and both genders.^{2,4,6,7} Outcome studies have identified factors such as absence of eschar, need for intensive care, age of 60 years or more, leucocytosis above 10000 cells/mm³ and hypoalbuminemia to be associated with severe complications and fatal outcomes in scrub typhus.^{8,9} In Indian studies, age and gender stratified profiles of scrub typhus have not been assessed. To explore this finding in Indian setting, we performed a pilot observation with study of clinical and laboratory profile stratified by age and

gender. We also evaluated differences in the duration of hospitalization and rates of complications in scrub typhus from single-centre in Central India.

METHODS

This retrospective, single-centre, pilot observational study was conducted at a private, tertiary hospital from Nagpur, India. We reviewed the data of patients admitted during May to August 2016. Scrub typhus cases diagnosed with positive IgM by enzyme linked immunosorbent assay (ELISA) test were included in analysis. Data on demography, clinical symptoms, signs, laboratory investigations and complication along with duration of hospital stay was assimilated from patient case files. Fever was defined as any fever with temperatures above 100⁰f.

Anaemia was defined as haemoglobin concentration below 11 gm/dL in both genders. Leucocytosis was considered with total leucocyte counts (TLC) above 15000 cells/mm³.

Thrombocytopenia was labelled when platelet counts were lower than 1.5 lac cells/mm³. Elevation in liver enzymes namely alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) 3 times above upper level of normal (for SGPT – 55 IU, for SGOT: 40 IU) was considered abnormal. Serum creatinine cut-off was taken as 1.5 mg/dL to consider renal function derangement.

Statistical analysis

Data was analysed with descriptive statistics. We performed gender and age stratified analysis of the study population. Two-sample t test was used to determine significance between continuous variables and Chi-square or Fischer exact test was used to compare categorical data. P value <0.05 was considered significant.

RESULTS

In 16 cases of IgM ELISA positive scrub typhus, median age was 35 years with majority being <40 years (68.8%), females (81.2%) and outstation residents (81.2%). Demographic characteristics are shown in Table 1.

Among various clinical symptoms, fever was seen all cases (100%) followed by nausea and/or vomiting (68.8%). Significantly higher proportion of females (84.6%) and patients aged <40 years (90.0%) had nausea/vomiting compared to their counterparts. Headache was 3rd most common symptom (56.2%) and was significantly higher in patients aged <40 years (80.0%).

Generalised maculopapular rash was evident only in one case. No patient had eschar development. Other

symptoms and the frequency by gender and age are described in Table 2. Uncommon symptoms like convulsion, loose stools were seen in females who were <40 years.

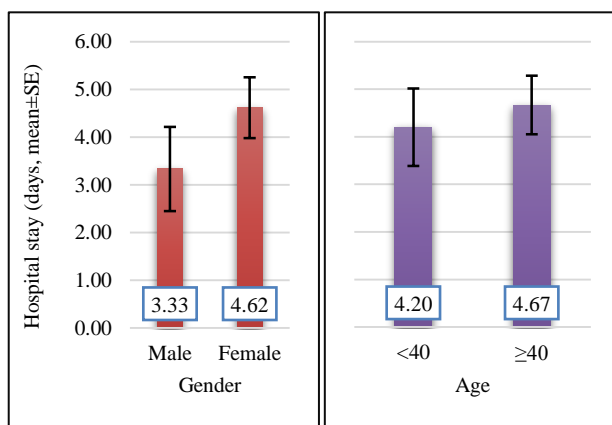
Males as compared to females (100.8±0.35 Vs 99.5±0.8 respectively; p<0.05) and patients above 40 years than <40 years (100.5±0.5 Vs 99.4±0.8 respectively; p<0.05) had higher mean temperature. Relative tachycardia was significantly higher in patients aged above 40 years.

Table 1: Baseline characteristics of study population.

| Characteristic | Observations (n=16) |
|-----------------------------|---------------------|
| Age (years) | |
| Median | 35 |
| <40 | 11 (68.8) |
| 40 to 60 | 3 (18.8) |
| >60 | 3 (18.8) |
| Gender | |
| Male | 3 (18.8) |
| Female | 13 (81.2) |
| Residence | |
| Local | 3 (18.8) |
| Outstation | 13 (81.2) |
| IgM ELISA Positivity | 16 (100.0) |

Data presented as median or n (%), SD: standard deviation, ELISA: Enzyme linked immunosorbent assay

No significant difference in systolic BP were seen among study groups but the diastolic BP was significantly lower in females than males (70.0±7.1 Vs 93.3±25.2, p<0.05). Other clinical signs did not differ among groups as shown in Table 2. Mean hospital stay in overall population was 4.38±2.2 days (median 4 days; range 1 to 10 days) which did not vary in gender- or age-specific analysis (Figure 1).



Numbers in bracket represent mean value and error bars represent the standard error of mean.

Figure 1: Duration of hospitalization by gender and age of study population.

Among laboratory parameters, mean haemoglobin of overall population was in anemia range (10.5±1.6 gm%)

with significantly lower level in females than females (10.1±1.4 vs 12.3±1.1 respectively, p<0.05). Mean levels of leucocyte count, platelet count, total bilirubin, liver

enzymes, serum creatinine and blood urea did not differ in any studied groups (Table 3).

Table 2: Clinical presentation of scrub typhus.

| Clinical Features | Total (n=16) | Gender | | Age | |
|-------------------------|-----------------|------------|---------------|------------|--------------|
| | | Male (n=3) | Female (n=13) | <40 (n=10) | ≥40 (n=6) |
| Symptoms | | | | | |
| Fever ^a | 16 (100.0) | 3 (100.0) | 13 (100.0) | 10 (100.0) | 6 (100.0) |
| Nausea/vomiting | 11 (68.8) | 0 | 11 (84.6) * | 9 (90.0) | 2 (33.3) * |
| Headache | 9 (56.2) | 2 (66.7) | 7 (53.8) | 8 (80.0) | 1 (16.7) * |
| Abdominal pain | 8 (50.0) | 1 (33.3) | 7 (53.8) | 5 (50.0) | 3 (50.0) |
| Cough | 6 (37.5) | 1 (33.3) | 5 (38.5) | 3 (30.0) | 3 (50.0) |
| Breathlessness | 6 (37.5) | 2 (66.7) | 4 (30.7) | 2 (20.0) | 4 (66.7) |
| Myalgia | 4 (25.0) | 0 | 4 (30.7) | 3 (30.0) | 1 (16.7) |
| Chest pain | 2 (12.5) | 1 (33.3) | 1 (7.7) | 1 (10.0) | 1 (16.7) |
| Joint pain | 2 (12.5) | 1 (33.3) | 1 (7.7) | 1 (10.0) | 1 (16.7) |
| Giddiness | 2 (12.5) | 0 | 2 (15.4) | 2 (20.0) | 0 |
| Generalised rash | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Weakness | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Loose motion | 1 (6.2) | 0 | 1 (7.7) | 0 | 1 (16.7) |
| Convulsion | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Burning Micturition | 1 (6.2) | 1 (33.3) | 0 | 0 | 1 (16.7) |
| Signs | | | | | |
| Temperature (0F) | 99.7±0.9 | 100.8±0.35 | 99.5±0.8 * | 99.4±0.8 | 100.5±0.5 * |
| Pulse rate (per minute) | 99.3±15.1 | 108.0±11.1 | 97.2±15.5 | 93.2±11.7 | 109.3±15.6 * |
| Systolic BP (mmHg) | 122.2±25.8 | 146.7±47.3 | 116.5±16.6 | 113.4±14.3 | 136.7±35.0 |
| Diastolic BP (mmHg) | 74.4±14.6 | 93.3±25.2 | 70.0±7.1 * | 69.0±7.4 | 83.3±19.7 |
| Pallor | 8 (50.0) | 1 (33.3) | 6 (46.2) | 5 (50.0) | 3 (50.0) |
| Icterus | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Lymphadenopathy | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Hepato-splenomegaly | 8 (50.0) | 2 (66.7) | 6 (46.2) | 5 (50.0) | 3 (50.0) |
| Ascites | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Edema feet | 2 (12.5) | 0 | 2 (15.4) | 1 (10.0) | 1 (16.7) |

Data presented as mean±SD or n (%), a: Fever duration (median=10 days), *p<0.05 significant

Table 3: Laboratory investigational profile of scrub typhus.

| Laboratory Parameters | Total (n=16) | Gender | | Age | |
|--|-----------------|-------------|---------------|-------------|------------|
| | | Male (n=3) | Female (n=13) | <40 (n=10) | ≥40 (n=6) |
| Haemoglobin (gm%) | 10.5±1.6 | 12.3±1.1 | 10.1±1.4 * | 10.4±1.2 | 10.8±2.2 |
| Leucocyte count (x10 ³ cell/mm ³) | 11.5±8.8 | 9.7±5.5 | 11.9±9.5 | 12.2±10.1 | 10.2±6.4 |
| Leucocytosis (>15000 cells/mm ³) | 5 (31.2) | 1 (33.3) | 4 (30.7) | 4 (40.0) | 1 (16.7) |
| Platelet (x10 ⁵ cell/mm ³) | 1.9±1.1 | 1.7±0.9 | 1.9±1.2 | 1.9±1.1 | 1.9±1.2 |
| Total bilirubin (mg/dL) | 1.7±1.6 | 1.1±0.4 | 1.9±1.8 | 2.0±2.1 | 1.3±0.6 |
| SGOT (IU) | 125.8±76.5 | 141.0±124.0 | 122.0±67.6 | 122.3±85.7 | 131.0±67.4 |
| SGPT (IU) | 134.0±103.9 | 190.0±190.6 | 115.4±64.8 | 136.7±128.5 | 130.2±69.8 |
| Serum creatinine (mg/dL) | 1.1±0.4 | 1.5±0.6 | 0.95±0.16 * | 1.0±0.2 | 1.2±0.5 |
| Blood Urea (mg/dL) | 47.4±26.6 | 70.0±24.0 | 42.3±25.6 | 36.7±15.6 | 60.2±33.6 |

Complications identified in study patients are summarized in table 4. Anaemia was seen in 56.25% cases which were seen only in females (69.2%) and in

40.0% of patients below 40 years. Other complications were thrombocytopenia (56.2%), elevation of liver enzymes (37.5%), pleural effusion (37.5%), bilateral

pneumonitis (6.2%), pericardial effusion (6.2%), and renal parenchymal disease (6.2%). From total complications (n=34), females (88.2%) and patients aged

<40 years (73.5%) had higher frequency of complications.

Table 4: Complications in study population.

| Laboratory Parameters | Total (n=16) | Gender | | Age | |
|--|-----------------|------------|---------------|------------|-----------|
| | | Male (n=3) | Female (n=13) | <40 (n=10) | ≥40 (n=6) |
| Anaemia (Hb<11 gm%) | 9 (56.2) | 0 | 9 (69.2) | 7 (70.0) | 2 (33.3) |
| Thrombocytopenia (Platelet<1.5 lac/mm ³) | 9 (56.2) | 2 (66.7) | 7 (53.8) | 6 (60.0) | 3 (50.0) |
| Increased liver enzymes | 6 (37.5) | 1 (33.3) | 5 (38.5) | 4 (40.0) | 2 (33.3) |
| Pleural effusion | 6 (37.5) | 0 | 6 (46.2) | 5 (50.0) | 1 (16.7) |
| Bilateral pneumonitis | 1 (6.2) | 0 | 1 (7.7) | 0 | 1 (16.7) |
| Pericardial effusion | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Capillary leak syndrome | 1 (6.2) | 0 | 1 (7.7) | 1 (10.0) | 0 |
| Renal parenchymal disease | 1 (6.2) | 1 (33.3) | 0 | 1 (10.0) | 0 |
| Total | 34 | 4 (11.8) | 30 (88.2) | 25 (73.5) | 9 (26.5) |

DISCUSSION

In this pilot study, we found higher proportion of females and patients younger than 40 years being diagnosed with scrub typhus. In an outbreak report from Rajasthan India, Sinha et al. reported scrub typhus in more number of females than males (66.7% Vs 33.3% respectively).² However, in previous studies there was no difference in prevalence of scrub typhus in males and females.^{3,6,7} Fever is almost universal in these cases and was seen in all cases in our study. Fever can be of short (<7 days) or long (>7 days) duration. Rama et al. reported 28% and 72% cases with fever of short and long duration respectively.⁴

Median fever duration in our study was 10 days. Clinical presentation present study was similar to previous reports of scrub typhus from all around India.^{4,6,10} Nausea with or without vomiting was significantly higher in females and younger patients whereas headache found in significantly higher proportion of young patients. Among clinical signs, a higher degree of temperature in males than females and in older patients along higher relative tachycardia in older patients were statistically significant observations. Such symptomatic association to gender and age need further exploration.

Eschar is a characteristic sign of scrub typhus and has been reported in various studies. None of the patient in our study had eschar formation. This pathognomic sign is seen at the inoculating site. Eschar detection of up to 45% cases have been reported.¹¹ In a similar series of 10 paediatric cases from Rajasthan, Gupta et al. have reported eschar in 2 cases.¹² A study from South India reported eschar in 46% cases.¹ Absence of eschar however should not exclude the diagnosis of scrub typhus. Interestingly, a study from Korea reported absence of eschar as a factor associated with severe scrub

typhus (odds ratio [OR] 6.62, 95% confidence interval 1.22, 35.8; p=0.03) on a multivariate analysis.

The other factors with significant association to severe disease were age above 60 years (OR 3.13), leucocytosis (OR 3.6), and hypoalbuminemia (serum albumin ≤3 gm/dL) (OR 5.01). We observed 18.8% cases above 60 years, no eschar in any patient, and leucocytosis in 31.2% cases. These purport that complete investigation of scrub typhus fever is necessary to determine factors associated with adverse outcomes. In our study we found anaemia (56.2%) and thrombocytopenia (56.2%) as most common complications. Rama et al also reported occurrence of thrombocytopenia in 56% cases which is similar to our study.⁴ Raised liver enzymes, pleural effusion, pneumonitis, capillary leak syndrome and renal disease were few of the complications seen in our study.

Such complications have been reported previously also. A study from Vivekanandan et al from South India reported thrombocytopenia in 28.1% and raised liver enzymes in 95.9% of the cases.¹ Such complications carry a higher risk of mortality in scrub typhus. In a multivariate analysis, Chrispal et al observed acute respiratory distress syndrome, shock, renal failure and metabolic acidosis as independent predictors of mortality.¹¹ Higher occurrence of complications in young females in our study is probably an incidental finding and requires further evaluation. Despite these observations, no significant difference in hospital stay was seen either in gender or age based analysis. No mortality was seen in any case in our study.

Limitations

Our study was limited by a retrospective design and limited number of cases. As we attempted age and gender specific analysis in such small sample, results can't be

generalised. These need further evaluation in a large sample prospective study. Evaluation of factors associated with complications was not performed in our study.

CONCLUSION

Our pilot observation in scrub typhus suggests higher frequency in females and in younger patients. Clinical profile was similar to other reports from various parts of India. Absence of eschar in doesn't exclude the diagnosis of scrub typhus. Laboratory abnormalities like anaemia, leucocytosis, thrombocytopenia and raised liver enzymes were common. Associated complications tend to increase the risk of mortality in these cases which demands early identification and treatment. This pilot study is one of early observations from central India highlights need of further prospective research in this underdiagnosed and underreported disease.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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