Clinical profile and risk factors associated with severe scrub typhus infection among non-ICU patients in semi-urban south India

Sarah S. Premraj, K. Mayilananthi, Durga Krishnan, K. Padmanabhan & D. Rajasekaran

Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Chennai, India

ABSTRACT

Background & objectives: Scrub typhus is an emerging infectious disease that generally causes acute febrile illness, with disease spectrum ranging from mild illness to multiorgan dysfunction. This study aimed to report the clinical profile, complications and risk factors associated with severe illness in patients with scrub typhus, outside the intensive care setting.

Methods: It was a prospective study, which involved recruitment of patients with acute febrile illness and diagnosed to have scrub typhus, who were admitted to the general medical wards of a tertiary care centre in Kanchipuram district, in semi-urban south India, over a 12 month period between June 2015 and May 2016. The diagnosis was established both clinically (with or without pathognomonic eschar) and by a positive test of IgM antibodies against scrub typhus by ELISA. The severity of scrub typhus was determined by the presence of organ dysfunction, and the factors associated with it were analyzed.

Results: A total of 50 patients with mean age of 39.6±20.5 yr (mean ± SD) were admitted. The mean duration of illness before presentation was 9.10 ± 8.6 days. The mean duration of hospital stay was 7.7±3.6 days. The symptoms included fever, abdominal symptoms, headache, dysuria, breathlessness and altered sensorium. Most common findings on physical examination were eschar (58%), crepitations in the chest (36%), hepatomegaly (34%) and lymphadenopathy (30%). Thirty two percent had respiratory complications, 4% required mechanical ventilation, 24% had shock, 16% had acute kidney injury, and 6% had dysfunction of ≥2 organs. Age of >50 yr, longer duration of illness (>7 days), residence in a rural area and the absence of eschar were found to be independent risk factors for development of severe illness.

Interpretation & conclusion: Severe scrub typhus infection among non-ICU patients is more likely to occur in elderly patients and in those with longer duration of illness prior to presentation. The subset of patients without eschar might be more prone to develop complications.

Key words: Eschar; ICU; risk factors; scrub typhus

INTRODUCTION

Scrub typhus is one of the important causes of acute undifferentiated febrile illness, which has garnered attention in the past decade. It is a re-emerging infectious disease in India and has gained clinical importance because of its effect on multiple organ systems and progression to various complications, when not detected early and managed appropriately. The presence of non-specific clinical features, which overlap with other common tropical fevers, makes the diagnosis challenging, owing to which, many patients develop life-threatening complications, and succumb to severe illness. The availability of safe and highly efficacious drugs promises a speedy recovery from illness, provided treatment is initiated promptly. Hence, it becomes necessary to define the clinical characteristics and laboratory features which aid in predicting the severity of the disease.

Most of the studies done so far have focused on the risk factors for development of complications in patients with scrub typhus in the intensive care unit (ICU). The present study aimed to define the clinical and laboratory profile of patients presenting with severe scrub typhus but not requiring ICU care, and to determine the risk factors associated with severity of illness in this subset.

MATERIAL & METHODS

Study setting

It was a prospective study, which involved recruitment of all patients with acute febrile illness diagnosed to have scrub typhus, clinically (with or without the pathognomonic eschar) and in the laboratory by a positive test of IgM antibodies against scrub typhus by ELISA method, who were admitted to the general medical wards...
of Chettinad Hospital and Research Institute, a tertiary care center in Kanchipuram district, in semi-urban South India, over a 12-month period between June 2015 and May 2016.

Patients with other causes of febrile illness such as dengue, malaria, typhoid and other bacterial infections, as well as those with mixed infections were excluded from the study. The patients directly admitted to the intensive care unit were also not included in the study.

Data compilation/Documentation

Baseline demographic details of the patients were documented; the presenting clinical features and duration of symptoms prior to hospital admission were noted. Vital signs were monitored and thorough physical examination was carried out for each patient. The patients were followed up till discharge from the hospital.

Variables studied

The severity of scrub typhus was determined by the presence of organ dysfunction, and the factors associated with it, were analyzed. Severe scrub typhus was defined if patients showed any of the following conditions: (i) Acute respiratory distress syndrome (ARDS) defined as new or worsening respiratory symptoms, with opacities on chest radiograph, not attributable to other causes of alveolar edema, with \( \frac{P_{\text{aO}_2}}{F_{\text{iO}_2}} < 300 \text{ mmHg} \) (Berlin definition)\(^1\); (ii) Renal failure, with estimated GFR less than 60 ml/min using the Cockcroft-Gault formula; (iii) Meningoencephalitis including altered mental states such as confusion, coma or other neurological deficits with no other evident causes; (iv) Shock, defined by a systolic blood pressure, \(< 90 \text{ mmHg} \) (or a fall in systolic blood pressure of \( > 40 \text{ mmHg} \)) or a mean arterial pressure of \(< 70 \text{ mmHg} \); (v) Myocarditis; (vi) Thrombocytopenia defined as platelet count \(< 100 \times 10^9/\text{l} \), with or without bleeding manifestations; and (vii) Hepatic dysfunction evidenced by increase in serum bilirubin \( > 2 \text{ mg/dl} \) or a two-fold increase in levels of hepatic transaminases.

Statistical methods

Statistical analysis was done using SPSS version 21. Descriptive statistics were obtained for all study variables. All categorical variables were compared using Chi-square and Fisher’s exact test and continuous variables were analyzed using Student’s \( t \)-test. All data were expressed as mean (±SD). Multivariate logistic regression analysis was used to determine the predictors of severity of illness. A \( p \)-value \( < 0.05 \) was considered as statistically significant.

RESULTS

During the study period of 12 months, 558 patients presenting with an acute febrile illness were screened and a total of 50 patients with scrub typhus were included in the study (8.96%). These patients were diagnosed to have scrub typhus based on a positive IgM ELISA assay results and/or the presence of a characteristic eschar. Other causes of febrile illness were ruled out.

Baseline characteristics

The baseline characteristics and initial presenting clinical features are summarized in Table 1. The mean age of the patients was found to be 39.6±20.5 yr (mean±SD), of which 62% were females. More than 2/3rd of the patients were from semi-urban and urban areas. The mean duration of illness was 9.10 ± 8.6 days before presentation.

Fever was observed in all the patients. Abdominal symptoms such as abdominal pain, nausea, vomiting or diarrhoea (46%), headache (36%), dysuria (24%), breathlessness (10%) and altered sensorium (2%) were the most common presenting symptoms. About 58% had an eschar, 30% had lymphadenopathy, and 36% were found to have crepitations in the chest. Other frequently encountered...
findings on physical examination were congestion of eyes, icterus, hepatomegaly, splenomegaly and altered sensorium. One patient had features of cerebellar dysfunction.

**Laboratory parameters**

The profile of laboratory investigations is shown in Table 2. Among the haematological parameters, thrombocytopenia was the most frequently observed finding (52%), while leucocytosis was seen in 40% of the patients. Biochemically, hyponatraemia was the commonest abnormality with 62% having a sodium value of <130 mEq/L. Renal failure was observed in 16%, and transaminitis was noted in 82% (mean AST 111± 96 IU/L; ALT 107± 84 IU/L).

**Organ dysfunction**

All patients were assessed for the presence and severity of organ dysfunction. Half of the patients had no organ dysfunction either at presentation or during stay in hospital. Twenty patients (40%) had one organ dysfunction, three (6%) with two-organ dysfunction, and only two (4%) had dysfunction of three or more organs. Among the complications, ARDS was predominant (32%), while shock was observed in 24% of patients, 16% had acute kidney injury, and CNS dysfunction was seen in 2% of the cases. Other complications included hyponatremia, thrombocytopenia and liver dysfunction. The profile of organ dysfunction is shown in Table 3. During the stay in hospital, three patients (6%) required admission to the ICU, one patient was kept mechanically ventilated, and 2% were initiated on inotropic support. The mean duration of hospital stay was 7.7± 3.6 days. In total, 49 patients (98%) recovered, and one was discharged against medical advice. In the present study, there was no mortality due to scrub typhus.

**Factors associated with severe scrub typhus**

The factors associated with the severity of infection were assessed by logistic regression analysis. Patients older than 50 yr were more likely to have thrombocytopenia (p = 0.027) and renal failure (p < 0.001). The duration of illness was also found to be correlated with the severity of disease. Patients with symptoms lasting for >7 days prior to presentation seemed more likely to develop ARDS [Odds Ratio 4.84 (95% CI; 1.32 – 17.67)] (p = 0.034). An important finding in the present study was that the absence of eschar was associated with more severe disease. Complications were found in 63.6% of those without eschar vs 42.8% of those with eschar (p = 0.008). Patients from rural and semi-urban areas were more prone to severe illness than their urban counterparts (p = 0.028). This may be due to delay in seeking healthcare or limited access to better health centers. No significant risk factors were found for the development of shock, liver involvement or CNS dysfunction. Patients were treated with either doxycycline (86%) or azithromycin (14%). The antibiotic used was at the discretion of the treating physician. The duration of hospital stay did not vary with respect to the presence of complications.

**DISCUSSION**

Several studies have been carried out on the magnitude of illness as well as predictors of mortality and severity of illness in scrub typhus. Most of these studies were conducted in the intensive care setting, involving patients with major organ dysfunction. The present study focuses on the patients with acute febrile illness, and diagnosed to have scrub typhus, admitted in the general medical wards, outside the intensive care setting. Since many such patients may be encountered by general practitioners in primary and secondary care centers, the factors which predict severity of illness in this subset of patients is important for further investigation. Knowledge of these risk factors will help the clinician to identify patients with higher risk of needing intensive care, and thereby monitor these patients closely for the development of organ dysfunction.

Among all the patients who presented with an acute febrile illness, 8.96% were found to have scrub typhus. This is comparable to other studies from India that have reported incidence ranging from 14.42 to 24%. In a community-based study from Vellore, south India, its
prevalence has been reported to be as high as 31.8%\textsuperscript{7}. The mean age of the patients in the present study was 39.6 yr, which is very similar to the study of Varghese et al\textsuperscript{8} from Vellore, and Jacob et al\textsuperscript{9} from Chennai, India where in the mean age was 36.5 and 30 yr, respectively. The mean duration of illness prior to presentation was 9.10 ± 8.6 days, while other studies reported duration ranging between 6 and 14 days\textsuperscript{8-9}. This indicates that, in patients who present with >1 wk of fever, scrub typhus should be high on the list of differential diagnoses. The clinical features were found to be non-specific and often overlapping with features of other tropical fevers. An eschar, which is characteristic of scrub typhus was found in 58% of the patients in the present study, similar to the incidence reported by other studies from geographically close areas\textsuperscript{7,8,13}. The primary objective of the present study was to define the complications in scrub typhus patients among non-ICU patients. Mild ARDS was the most frequently encountered complication in this study (32%). In a study from Meghalaya, India the reported incidence of ARDS was 29%, although the definition used for ARDS was somewhat different\textsuperscript{10}. It is interesting to note that most of the scrub typhus patients with mild ARDS, could be managed in the medical wards with antibiotics and appropriate supportive measures including oxygen and non-invasive ventilation, as only 4% patients in this study required invasive mechanical ventilation. Shock was found in 24%, which was fluid responsive in 98% of the cases and could be treated in the general ward, without the need for inotropes. One patient required inotropic support in the ICU. Another common complication was acute kidney injury (AKI), seen in 16% of the patients. Studies by Attur et al\textsuperscript{11} and Kumar et al\textsuperscript{12} have also demonstrated a higher incidence of AKI (23.2% and 53%, respectively) in scrub typhus patients. However, none of the patients in this study required dialysis. There was evidence of hepatoacellular dysfunction in a high number of patients (82%), which correlates with similarly high figures reported by Varghese et al\textsuperscript{13} (64.5%) and Vivekanandan et al\textsuperscript{14} (95.9%).

One of the primary objectives of this study was to identify the factors that predict the severity of illness in the non-ICU setting. It was found that older patients (>50 yr of age) had a higher likelihood of renal failure and thrombocytopenia, which was in agreement with a study by Karanth et al\textsuperscript{15}. Those who had a longer duration of fever (>7 days) were more prone to develop severe illness ($p=0.034$). Another noteworthy finding was that the absence of eschar was found to be associated with severe illness ($p=0.008$). These two factors can be linked together, presuming that the presence of an eschar leads to an early diagnosis of scrub typhus. On the other hand, scrub typhus without an eschar requires a high index of suspicion for diagnosis, and is often overlooked in the initial fever work-up. Therefore, those without an eschar were likely to have a longer duration of illness before presentation with a resultant increase in the complication rate. Similar observations were reported by Kim et al\textsuperscript{9} who hypothesized that the strains of Orientia tsutsugamushi causing scrub typhus without an eschar may be more virulent. Therefore, it is prudent to anticipate a higher rate of complications in the patients with eschar-negative scrub typhus. The study also found that patients hailing from rural areas had higher incidence of complications than those from urban areas. This may be attributed to the delay in accessing healthcare combined with the relatively low awareness regarding scrub typhus among general practitioners in those areas.

Although, many other studies have reported risk factors such as altered sensorium, leucocytosis, hypoalbuminemia, anaemia, hepatic dysfunction and hypotension for severe illness, the present study failed to demonstrate any significant impact of these variables\textsuperscript{4-5,16}. There was no mortality related to scrub typhus in this study. This implies that in non-ICU patients, early diagnosis of the infection, recognition of complications, and institution of antibiotic therapy with doxycline or azithromycin can aid in reducing mortality.

Based on the results of this study, the following observations need to be emphasized. Scrub typhus needs to be considered in the diagnosis of any patient presenting with an acute to sub-acute febrile illness. It can be found even in the urban and semi-urban population with no significant exposure to scrub vegetation. Further, the absence of an eschar does not rule out the infection, rather it may predict severe illness. Older patients and those with longer duration of illness must be closely observed for the development of complications. Early diagnosis and prompt treatment can minimize the severity of illness and prevent intensive care admissions even in patients with early organ dysfunction.

CONCLUSION

The study showed that scrub typhus can be associated with severe illness even outside the ICU setting. When scrub typhus patients are older, have a prolonged duration of illness prior to presentation, or present without an eschar, the severity of illness is likely to be higher. Clinicians should closely monitor such patients to minimize the risk of complications and to initiate intensive care treatment early.
Conflict of interest
The authors declare that they have no competing interests.

REFERENCES