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Original Research Article

Risk factors of acute respiratory distress syndrome in Scrub typhus

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ABSTRACT

Background: Scrub typhus is a common tropical infection presenting as acute febrile illness. Acute Respiratory Distress Syndrome (ARDS) is a serious complication of scrub typhus and is often associated with high mortality. This study was aimed to analyse risk factors of ARDS in Scrub typhus patients.
Methods: This study was a prospective observational case control study conducted from June 2012 to June 2015 in Kasturba Hospital, Manipal, Karnataka, India. ARDS was diagnosed as per Berlin criteria.
Results: During the study period, a total of 320 patients were diagnosed to have scrub typhus as per our criteria. All the patients were from state of Karnataka except for 1 patient, who was from state of Kerala. A total of 20 (6.25%) patients (cases) were diagnosed to have ARDS and 300 (93.75%) patients (controls) did not have ARDS. After multivariate analysis of the risk factors only two risk factors had significant association with development of ARDS: sepsis (OR 4.34,95% CI 0.51,36.76) and septic shock (OR 16.57 95% CI 1.64,166.76).
Conclusions: ARDS is a common and serious complication of scrub typhus. It often occurs along with other complications. Presence of dyspnoea, sepsis, septic shock, hypoalbuminemia should alert clinicians about ARDS. ARDS due to scrub typhus is associated with high mortality. Early recognition and prompt therapy can reduce mortality.

Keywords: ARDS, Risk factors, Scrub typhus

INTRODUCTION

Scrub typhus is a common tropical infection caused by *Orientia tsutsugamushi* (a gram-negative bacterium from the Rickettsiaeceae family) which is transmitted by the bite of a trombiculid mite.[1]

The disease is spread over an area called the tsutsugamushi triangle extending from northern Japan in the east to Pakistan and Afghanistan in the west and northern Australia in the south.[2] Symptoms include fever, headache, nausea, vomiting, shortness of breath, altered sensorium and myalgia. A pathognomonic eschar may be seen at the site of the chigger bite. Clinical course can range from a mild, self-limiting disease to a fatal illness with complications such as multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), meningoencephalitis, hepatitis, and myocarditis with shock.[3,4]

ARDS is a serious complication of scrub typhus and is often associated with high mortality.[4] Recognition of this complication of scrub typhus is important so as to initiate early treatment there by reducing the mortality

significantly. There is not much data on risk factors of ARDS complicating scrub typhus especially from the Indian subcontinent. This study was aimed to analyze risk factors of ARDS in scrub typhus patients.

METHODS

This study was a prospective observational case control study conducted from June 2012 to June 2015. This study was done in Kasturba Medical College, Manipal, Karnataka, India.

Inclusion criteria was in patients presenting with Acute Febrile Illness (AFI) aged ≥18 years. Clinically suspected to be suffering from scrub typhus. Scrub typhus was diagnosed by both serological and molecular tests. Serological tests constituted:

- Weil Felix (WF) test: the antigens for WF test, OX-K (FA/026), OX-2 (FA/022) and OX-19 (FA/024) were obtained from Plasmatec (Guatemala, CA). A titer of 1:160 was considered significant
- IgM ELISA: IgM ELISA kits (InBios International Inc, USA) detected IgM antibodies in the patient sera; results were recorded either as positive or negative and the cut off OD value fixed was fixed at 1.0
- M-IFA: M-IFA slides (OTM-120, Fullers laboratory, California, USA) were coated with standard antigens (Kato, Karp, Gilliam or Boryong) to detect IgM antibodies in the patient sera and processed slides were visualized under a fluorescent microscope; good fluorescence to any of the antigen dots was considered as positive.[5]

The molecular method was the N-PCR test in which the primers were based on the nucleotide sequence encoding the 56-kDa type specific antigen of the *O. tsutsugamushi*. The nested PCR constituted two round of amplification steps. If there was an amplified product of size 483-bp approximately, the sample was considered positive for scrub typhus.

Additional tests were done to rule out other common causes of AFI in India like malaria, dengue fever, leptospirosis, enteric fever, brucellosis and bacteremia.

A set of blood cultures were collected possibly prior to the initiation of antibiotic therapy and the bacteria if present were identified.

A diagnosis of ARDS was based on the criteria for ARDS of the American-European Consensus Committee also known as the Berlin criteria:

- Acute onset timing: within one week of a known insult or new/worsening respiratory symptoms
- Chest radiograph showing bilateral lung infiltrates which are not explained by other lung pathology
- Respiratory failure is not explained by volume overload or cardiac failure and
- Severe hypoxia with a decreased partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2/FiO2), regardless of the level of positive end-expiratory pressure (mild: 201-300mm Hg, moderate: 101-200mm Hg and severe: ≤100mm Hg).[6]

For this study, patients who presented with ARDS were defined as cases and those without ARDS as controls.

Statistical analysis was carried out using SPSS 15. Univariate analysis for continuous variables was deemed statistically significant by an independent-sample t-test or a Mann-Whitney U test whereas a chi-square test was used for dichromatic variables. Statistical significance was considered when p was <0.05.

RESULTS

During the study period, a total of 320 patients were diagnosed as scrub typhus. All the patients were from the state of Karnataka except for 1 patient, who was from the state of Kerala.

A total of 20 (6.25%) patients (cases) were diagnosed to have ARDS and 300 (93.75%) patients (controls) did not have ARDS. Risk factors with strong association with ARDS in descending order were: hypoalbuminemia (cases: 100%, controls: 64%, p value: 0.001), invasive ventilation (cases: 25%, controls: 5.2%, p value: 0.004), multiorgan dysfunction (cases: 25%, controls: 4.5%, p value: 0.04), sepsis (cases: 20%, controls: 3.5%, p value: 0.01) and septic shock (cases: 20%, controls: 1%, p value: 0.01) (Table 1).

After multivariate analysis of the risk factors only two risk factors had significant association with the development of ARDS:

Sepsis (OR 4.34,95% CI 0.51,36.76) and septic shock (OR is 16.57 95% CI 1.64,166.76).

Table 1: Univariate analysis of risk factors.

Parameter	Control	Case	P value
Eschar	74 (25.4%)	9 (45.0%)	0.054
Ventilator support	15 (5.2%)	5 (26.3%)	0.004
AKI	5 (1.7%)	0 (0.0%)	0.723
MODS	14 (4.7%)	5 (25.0%)	0.004

Meningitis	3 (1.0%)	0 (0.0%)	0.823
Meningoencephalitis	7 (2.3%)	1 (5.0%)	0.407
Sepsis	11 (3.7%)	4 (20.0%)	0.010
Septic Shock	3 (1.0%)	4 (20.0%)	0.000
Pneumonia	5 (1.7%)	0 (0.0%)	0.723
Myocarditis	2 (0.7%)	0 (0.0%)	0.879
Thrombocytopenia	179 (60.5%)	16 (84.2%)	0.168
Thrombocytosis	8 (2.7%)	0 (0.0%)	0.168
Elevated creatinine	37 (12.5%)	3 (15.8%)	0.600
Total Bilirubin	89 (30.2%)	11 (57.9%)	0.062
Elevated AST	252 (85.4%)	19 (100.0%)	0.277
Elevated ALT	184 (62.4%)	13 (68.4%)	0.884
Elevated ALP	159 (54.1%)	15 (78.9%)	0.140
Hypoalbuminemia	185 (64.0%)	19 (100.0%)	0.001

DISCUSSION

This prospective observational case control study had 20 patients (6.25%) with ARDS out of the 320 scrub typhus patients. In a study done in Vellore, India by Varghese et al, the incidence of ARDS in scrub typhus was 43.5% (67 out of the 154 cases with scrub typhus).[7] Another study done in Andhra Pradesh, India by Venkategowda et al, showed the incidence of ARDS in scrub typhus as 41.3% (24 out of 58 cases with scrub typhus) both of which are higher than the present study.[8]

The pulmonary manifestations of scrub typhus are usually pneumonitis, some of which progress to ARDS.[9] ARDS is a form of diffuse lung injury whose major risk factors apart from lung disease (aspiration pneumonia, infection, COPD) are sepsis, pancreatitis, massive transfusion, fat embolism, drowning and trauma. All these release inflammatory mediators which trigger the lung injury.[10] ARDS is also one of the complications of scrub typhus.[11] ARDS in scrub typhus could be due to proliferation of *O. tsutsugamushi* in the endothelial cells leading to vasculitis in the microvasculature of the lung as speculated by Strickman or it could be due to an immune mechanism with no evidence of vasculitis.[12,13] According to a review by Tsay et al, 44% of patients developed ARDS within 4-7 days of onset.[14]

After a multivariate analysis, we found that sepsis (OR 4.34,95% CI 0.51,36.76) and septic shock (OR 16.57 95% CI 1.64,166.76) were associated with increased chances of ARDS.

Based on univariate analysis, all of the cases had hypoalbuminemia which was statistically significant (p value= 0.001). As mentioned earlier, the pathology of scrub typhus involves proliferation of the organisms in the endothelial cell linings leading to infiltration of leukocytes which causes the vasculitis/perivasculitis of the microvasculature in various organ systems like lungs, brain, heart, kidney, spleen, lymph nodes, etc. This leads to increased vascular permeability causing increased extravascular protein loss which is the reason for hypoalbuminemia. A study by Song et al, showed that scrub typhus patients with hypoalbuminemia had an increased risk for lung effusions, interstitial pneumonitis and alveolar edema than those without hypoalbuminemia.[15] CS Lee et al, also found similar results.[16] This finding concurs with the present study. Cases with lung pathologies often lead onto ARDS.

The presence of an eschar in a patient is usually considered pathognomonic for scrub typhus. We found 45% of the scrub typhus patients with ARDS had an eschar. CS Lee et al, found after multivariate analysis in their study that the absence of eschar was an independent risk factor for a serious outcome.[17] Monitoring patients closely regardless of the presence or absence of eschar as well as to start treatment in a non-eschar patient with a strong suspicion of scrub typhus hence preventing serious complications.

According to a previous study by Wang et al, the incidence of ARDS in scrub typhus was 11.1% (8 of 72 patients) of which 2 died (mortality rate of 25%). In their study 8 patients with ARDS had high WBC counts, low hematocrit and high bilirubin as compared to the 64 patients without ARDS. Additionally, late commencement of antibiotics, low albumin levels and a prolonged PT time were found to be the risk factors for ARDS after multivariate analysis.[18] Tsay et al, had reported incidence of ARDS in scrub typhus as 15% (5 of 33 patients). According to this study the presence of early pneumonitis, older age and thrombocytopenia are risk factors for ARDS in scrub typhus.[14]

We observed that three patients with ARDS died (mortality rate of 15%) which is within the observed range of the mortality rate (0-70% with a median of 6%).[11] This high mortality rate could be due to delay in diagnosis, late referral and delay in administration of appropriate antibiotics.

The limitations of our study could be that the study is single center study and could have had referral bias.

CONCLUSION

In conclusion patients with scrub typhus with risk factors must be actively monitored for impending ARDS.

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