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Assessment of Predictors for Severity in Scrub Typhus-A Case-Control Study

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ABSTRACT

Objective: Scrub typhus is a rickettsial febrile condition caused by bacteria called Orientia tsusugamushi. It spreads to people through bites of infected chiggers (larval mites). The objective of this study was to know the predictors of severity in scrub typhus. Methods: A case-control study was done at Kasturba Medical College Hospital (2012-2015) retrospectively on patients admitted with scrub typhus. Patient demographics, lab parameters, investigations and treatment courses were noted. Subjects were divided into two groups, non-severe and severe group. Patient clinical details and laboratory parameters were compared in both the groups. The lab parameters associated with the severity of disease and mortality were also analyzed. A total of 210 patients out of which 140 controls (non-severe group) and 70 were cases (severe group). Results: The overall mortality due to scrub typhus infection was 14.3%. Eschar was present in 21.4% of the patients. Among the cases, the common symptoms were cough, chest pain, abdominal pain and distension, pedal edema and facial puffiness. Lymphadenopathy was observed with non-severe cases of scrub typhus and was statistically significant whereas, icterus, maculopapular rash, and hepatomegaly were associated with severe scrub typhus infection. Hemoglobin, platelet count and serum albumin were considerably lower in patients who died, whereas AST, aPTT, serum urea and creatinine were higher in them. Conclusion: Lower levels of hemoglobin, platelet count, serum albumin and higher levels of total leucocyte count, hepatic transaminases and serum creatinine correlated with severity. Doctors need to be watchful for such lab parameters and act quickly.

Keywords: Fever, Multi-Organ dysfunction syndrome, *Orientia tsutsugamushi*, Rickettsia

INTRODUCTION

Scrub typhus is a common febrile condition caused by the bite of larval mites infected with *Orientia tsutsugamushi* [1]. It starts with a headache and mild fever. When severe can present with various complications like meningo-encephalitis, acute kidney injury, hepatic dysfunction, thrombocytopenia, Acute respiratory distress syndrome (ARDS) or myocarditis. Clinically splenomegaly, lymphadenopathy, conjunctival infection, maculopapular rash, and eschar are evident. However, they can also present with complications like thrombocytopenia, acute kidney injury (AKI), hepatic dysfunction, pneumonitis, meningo-encephalitis and disseminated intravascular coagulation [2,3]. The disease has high mortality rates which need immediate intervention. Few studies exist for scrub typhus severity by laboratory markers [4,5]. Hence we intended to do this study to explore new possible markers associated with severity in scrub typhus infection.

MATERIALS AND METHODS

Ethical Committee approval was taken prior to starting the study. The study was a case-control study done retrospectively. Data were obtained and analyzed from the case sheets and treatment chart of scrub typhus patients treated in the Medicine Department from January 2012 to December 2015 (approximately 70 cases and 140 controls). The

outcome of all the patients was recorded. Patients aged ≥ 18 years of age with a positive serological test (Scrub IgM ELISA) and high titers of Weil-Felix (>1:320) were included. Those patients with pre-existing renal failure, chronic liver disease, immune thrombocytopenic purpura, bleeding disorders and who did not undergo complete treatment (discharge against medical advice) were excluded from the study. The diagnosis was done on the basis of standard guidelines which has nine criteria [6,7]. If the patient had any of the 9 features, he/she would be classified as having severe scrub typhus. Patients with a positive diagnosis were then divided into case and control with former having severe scrub typhus.

Statistical Analysis

SPSS software (version 15) was used for data analysis. Continuous variables that were normally distributed were summarized by descriptive statistics. Median and inter-quartile range (IQR) were used to summarize the skewed continuous variables. Mann-Whitney and Chi-square tests were used. Tests with p-value <0.05 were considered statistically significant.

RESULTS

Patient baseline characteristics are given in Table 1. Male predominance was noted in both the groups (cases and controls i.e. 55.7% and 60% respectively). Duration of fever was slightly more in cases (8 days) than in controls (7 days). Eschar was present in more percentage of cases (25.7%) compared to controls (19.3%). The symptoms in the two groups are presented in Table 2. Headache and anorexia were the symptoms found to be more common among the controls. Among the cases, the common symptoms were cough, chest pain, abdominal pain and distension, pedal edema and facial puffiness. After analyzing the signs in scrub typhus, lymphadenopathy was commonly associated with the control group i.e. non-severe scrub typhus, whereas icterus, maculopapular rash and hepatomegaly were associated with severe scrub typhus infection. As shown in Table 3, among the biochemical parameters: hemoglobin, platelet count and albumin were significantly lower among the cases compared to the controls. The total leucocyte count, total and direct bilirubin, transaminases, International normalized ratio, aPTT, serum urea, and serum creatinine were higher in cases compared to controls. Proteinuria was present more in cases compared to controls i.e. 58.6% and 31.4% respectively and the p-value was significant.

Table 1 Baseline characteristics of the subjects

Variable	Result	
	Cases (n=70)	Controls (n=140)
Age, median (IQR)	47 (32.8-55)	35 (28-49.8)
Males	39 (55.7%)	84 (60%)
Females	31 (44.3%)	56 (40%)
Duration of fever in days, median (IQR)	8 (5-10)	7 (6.8-10)
Eschar Present	18 (25.7%)	27 (19.3%)
Absent	52 (74.3%)	113 (80.7%)

Table 2 Comparison of the symptoms and signs in cases and controls

Symptoms	Cases (n=70)	Controls (n=140)	p-value
Fever	69 (98.6%)	140 (100%)	0.156
Headache	15 (21.4%)	76 (54.3%)	<0.001
Vomiting	24 (34.3%)	42 (30%)	0.528
Anorexia	4 (5.7%)	27 (19.3%)	0.009
Chest pain	2 (2.9%)	0 (0%)	0.044
Cough	19 (27.1%)	18 (12.9%)	0.037
Myalgia	17 (24.3%)	51 (36.4%)	0.076
Abdominal pain	22 (31.4%)	25 (17.9%)	0.026
Arthralgia	2 (2.9%)	7 (5%)	0.47
Abdominal distension	2 (2.9%)	0 (0%)	0.044
Pedal edema	5 (7.1%)	0 (0%)	0.001
Puffiness of face	4 (5.7%)	0 (0%)	0.004

Diarrhea	6 (8.6%)	12 (8.6%)	1
Lymphadenopathy	7 (10%)	31 (22.1%)	0.031
Icterus	33 (47.1%)	13 (9.3%)	<0.001
Conjunctival injection	11 (15.7%)	16 (11.4%)	0.382
Eschar	18 (25.7%)	27 (19.3%)	0.285
Rash (maculopapular)	14 (20%)	13 (9.3%)	0.029
Splenomegaly	32 (45.7%)	67 (47.9%)	0.769
Hepatomegaly	40 (57.1%)	53 (37.9%)	0.008
*Chi-square test applied			

Table 3 Comparison of biochemical parameters in cases and controls

Biochemical Parameters, Median (IQR)	Cases (n=70)	Control (n=140)	p-value
Total leucocyte count (count/ml)	11400 (8200-16450)	7600 (5300-10800)	<0.001
Haemoglobin (g/dl)	11.4 (9.7-13)	12.2 (11.1-13.2)	0.009
Platelet count (count/ml)	49500 (21750-96750)	154000 (89250-215250)	<0.001
Erythrocyte sedimentation rate (mm/hr)	41.5 (16-59.3)	45 (23.3-60.8)	0.25
Direct bilirubin (mg/dl)	2.9 (1.0-5.8)	0.2 (0.2-0.5)	<0.001
Total bilirubin (mg/dl)	3.4 (1.5-6.7)	0.6 (0.4-1.1)	<0.001
Serum albumin (g/dl)	2.5 (2.3-2.8)	3.4 (3.0-3.8)	<0.001
Aspartate transaminase (IU/L)	184.5 (129.8-267.5)	74 (48.3-102)	<0.001
Alanine transaminase (IU/L)	111 (78.3-149.3)	69 (46.3-96)	<0.001
Alkaline phosphatase (IU/L)	233.5 (175.5-349.5)	122.5 (80-200.1)	<0.001
International normalized ratio	1.29 (1.18-1.46)	1.10 (1.01-1.16)	<0.001
aPTT (seconds)	46.9 (41-54.9)	35.8 (31.5-40.4)	<0.001
Serum creatinine (mg/dl)	1.7 (0.98-3.6)	0.8 (0.7-1.0)	<0.001
Serum urea (mg/dl)	84 (43.3-144.8)	24 (18-32)	<0.001
*Mann-Whitney test applied			

As shown in Figure 1, the common causes of death among the cases were multi-organ dysfunction syndrome (MODS) which accounted for approximately 31% of deaths followed by ARDS and AKI. There were 30 (43%) deaths among the cases i.e. patients with severe scrub typhus infection. Table 4 depicts the biochemical parameters of cases who survived or died. Hemoglobin, platelet count and serum albumin were found to be low in patients who died, whereas AST, aPTT, serum urea and creatinine were higher in the same group of patients.

Table 4 Comparison of biochemical parameters among cases who died and those who survived

Biochemical Parameters, Median (IQR)	Cases who died (n=30)	Cases who survived (n=40)	p-value
Total leucocyte count (count/ml)	11250 (6875-16450)	11650 (8925-16800)	0.502
Hemoglobin (g/dl)	10.4 (8.4-11.9)	11.9 (10.7-13.6)	0.001
Platelet count (count/ml)	36000 (20725-52250)	76500 (22750-132000)	0.01
Erythrocyte sedimentation rate (mm/hr)	48.5 (26.3-60.8)	34 (14.5-57.8)	0.194
Direct bilirubin (mg/dl)	3.7 (0.9-4.8)	2.25 (1.0-6.2)	0.835
Total bilirubin (mg/dl)	4.3 (1.5-5.5)	3.1 (1.4-7.2)	0.91
Serum albumin (g/dl)	2.4 (2.2-2.5)	2.7 (2.3-3.0)	0.023
Aspartate transaminase (IU/L)	221.5 (158-326.3)	160 (125.3-226.5)	0.037
Alanine transaminase (IU/L)	98.5 (51.8-150.5)	116 (98.3-145.3)	0.119
Alkaline phosphatase (IU/L)	244 (153.3-402)	228.5 (178.8-326.8)	0.939
International normalized ratio	1.37 (1.2-1.5)	1.25 (1.15-1.40)	0.184
aPTT (seconds)	53.1 (46.5-58.9)	45.2 (38.8-51.4)	0.003
Serum creatinine (mg/dl)	2.85 (2-4.95)	1.15 (0.80-1.78)	<0.001
Serum urea (mg/dl)	117 (73.8-177.5)	57.5 (29.5-112.8)	<0.001
*Mann-Whitney test applied			

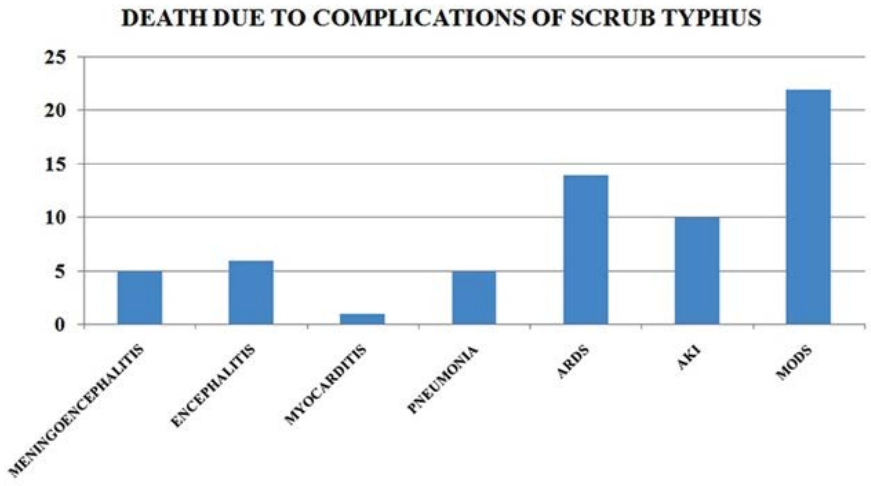

Figure 1 Causes of death in severe Scrub typhus

DISCUSSION

Scrub typhus is a treatable disease but if not diagnosed and treated early may result in complications. These patients may have an eschar which is quite characteristic of this disease. In our study, 21.4% of the patients had eschar. Other studies have shown an eschar detection rate of 46%-86% [8]. Weil-Felix has high specificity but low sensitivity to diagnose scrub typhus. Positive Weil-Felix test is defined as a single serum sample titers of >1:320 [9,10]. In the Indian subcontinent, severe scrub typhus causing mortality was approximately 14% as seen in one other study by Varghese, et al., [5]. In our study, mortality was 42.8% in severe scrub typhus group which could have been due to delay in the presentation to our hospital. Obligate intracellular nature of *O. tsutsugamushi*, rapidly dividing in the endothelium of blood vessels is probably the reason for the severity of disease in scrub typhus [11]. During the acute phase, there is a release of a number of immune cytokines and the levels of these are said to positively correlate with severity of disease [12].

The mean age at presentation was 45 ± 14.65 years in the severe group and 39 ± 13.5 years in the non-severe group with no statistical significance. Recreational or occupational activities are more in this age group i.e. between 30-50 years of age, which subjects them to risk of developing the disease [13]. On univariate analysis taking age >50 years as a risk factor for severity, we found no statistical significance between the two groups. However, Kim et al. in his study found that age >60 years was a predictor of severity [14]. In our study, overall mortality was 14.3%. As per a study done by Watt, et al., mortality varied from 15%-30% [15].

Incidence of ARDS is 8%-10% in India [16]. The study by Varghese, et al., [5] and Wang, et al., [17] reported the case fatality rate with ARDS of 18% and 25% respectively. However, in our study, the incidence of ARDS was 19% with a case fatality rate of 35%. Attur et al. [18] found the incidence of AKI to be 23.2%, whereas in our study it was 19%. The incidence of meningoencephalitis of 6.7% in our study is lower than the rest of the studies from India which have reported 9.5% and 14% [16,19]. The absence of eschar was found to be an independent predictive variable leading to fatal outcomes in some studies [14,20]. However, in our study, it was not found to be significant. Eschar was present in 21.4% of patients in this study. Vivekanandan, et al., in Pondicherry reported the presence of eschar in 46% of patients [19] whereas, it was seen in only 9.5% of patients as reported by Mahajan, et al., in North India [16]. The variation maybe because of the different geographic distribution or warranting future research [21].

There was significant thrombocytopenia observed in our patients with severe scrub typhus as shown in Table 3. A study done in South India observed thrombocytopenia in 60% of the subjects [8]. Leukocytosis i.e. WBC count >10,000 mm^3 noted with severe scrub typhus infection in our study as shown in Table 3. Kim, et al., [14] and Lee, et al., [20] also observed leukocytosis in severe group suggesting serious infection. We observed anemia (hemoglobin >12 g/dl) to be a predictor of severe scrub typhus, which is in agreement to study done by Suman, et al., [13] and contrary to study done by Kim, et al., [14], who failed to demonstrate anemia as an independent risk factor. Serum creatinine of greater

than 1.4 mg/dl was an independent predictor of severity as per a study done in South India which is in agreement with the results of our study [22]. The severe scrub typhus group had lower albumin levels $p<0.05$ (Table 3), which was also demonstrated by Kim, et al., as a predictor of severity of disease [14]. Increased vascular permeability due to damaged endothelial cells as a consequence of a disseminated vasculitic process led to extravascular leakage of proteins causing hypoalbuminemia [23]. A high level of hepatic transaminases in scrub typhus has been found in some studies [24]. There was a significant difference in the magnitude of AST/ALT levels between severe cases and non-severe cases in our study but a report conducted by Kim et al. did not support this finding [14].

The study had few limitations. The scrub typhus burden in the community is not represented here since it is a hospital-based study. Being retrospective and single centered results cannot be generalized. Because of the methodology selected, it might have led to bias in the selection of patients and lack of medical information of some patients which would have helped us get more patients. We also do not have the follow-up data of all these patients after discharge. Variation of strain and virulence is correlated to the severity of scrub typhus. This warrants the necessity of studies focusing on the clinical profile of circulating strain.

CONCLUSION

Scrub typhus is a commonly seen febrile illness in India which has high rates of mortality. Systemic complications are common with scrub typhus if not diagnosed and treated early. MODS and ARDS are two important causes of mortality. Presence of anemia, leukocytosis, thrombocytopenia, raised transaminase levels, raised serum creatinine and low albumin levels among patients presenting with acute febrile illness in endemic settings should warrant testing for scrub typhus and initiate treatment early to prevent complications. It is also important to rule out co-endemic diseases like malaria, leptospirosis, and dengue which have a similar presentation. Severe complications and mortality in scrub typhus could be prevented by close observation and monitoring of the patients who have the potential for complications and diagnosing them early with early initiation of therapy.

DECLARATIONS

Data Availability

No data were used to support this study.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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