ORIGINAL ARTICLE

Factors for Severe Outcome in Scrub Typhus: A Hospital Based Study in Sub Himalayan Region

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Abstract

Background: Scrub typhus is a re-emerging zoonotic rickettsial infection. Mortality is approximately 15% in some areas due to missed or delayed diagnosis. There had been only few studies on the markers for the severity of the disease, so this study has been planned to provide the knowledge regarding various aspects of scrub typhus in adult age group to detect early signs of severity.

Methods: All the patients more than 18 years of age admitted with febrile illness with positive IgM ELISA for scrub typhus with or without eschar were included in the study. The clinical profile was observed. The predictors of mortality were explored using univariate and multivariate analysis.

Results: On linear regression analysis and logistic regression analysis altered sensorium, low serum albumin, hepatic dysfunction, renal dysfunction, septic shock, MODS, ARDS, duration of fever > 7 days, day of receiving treatment > 7 days at presentation were significantly associated with high in- hospital mortality.

Conclusion: Early treatment with doxycycline should be instituted at the clinical suspicion of scrub pending investigation as it is life saving. Close follow up of the patient should be done to indentify subtle signs of organ dysfunction to start early supportive treatment.

Introduction

The present study is a part of our study published in JAPI, 2016 focussing on the factors responsible for severe outcome in scrub typhus patients. Scrub typhus is a re-emerging zoonotic rickettsial infection[1,2] and it is characterized by focal or disseminated vasculitis and perivasculitis which may involve the lungs, heart, liver, spleen and central nervous system. Clinical manifestations involve almost every organ and can range in severity from a mild, self-limiting disease to, if untreated, a fatal illness.[3] The complications that can be seen in patients with scrub typhus are jaundice, pneumonitis, acute respiratory distress syndrome (ARDS), septic shock, renal failure, myocarditis, meningoencephalitis and multiorgan dysfunction syndrome (MODS) may be the presenting manifestation after the first week of illness.[4,5] Mortality rates in untreated patients range from 0-30%. In the pre-antibiotic era, mortality rates averaged 11-30%. However, mortality is still approximately 15% in some areas due to missed or delayed diagnosis.[6] There had been only few studies on the markers for the severity of the disease, so this study has been planned to provide the knowledge regarding various aspects of scrub typhus in adult age group to detect early signs of severity.

Methodology

This was an prospective observational study done in the department of Medicine and Microbiology IGMC, Shimla from July 2012 to June 2013. All the patients more than 18 years of age admitted with febrile illness with positive IgM ELISA for scrub typhus with or without eschar were included in the study. The clinical profile was observed using a detailed history of symptoms, travel, recreation, agricultural activities, treatment record prior to admission and a detailed examination and treatment outcome was noted. Basic biochemical tests, ABG and fever workup including cultures, CXR, CSF analysis, serology for scrub was done. IgM scrub typhus was done by kit method manufactured by InBios International, Inc. This was a qualitative ELISA for the detection of IgM antibodies to O. tsutsugamushi in serum. Statistical analysis was done using EPI info 2000 (Centre of Disease Control and Prevention, Atlanta, GA, USA) and SPSS student version 16.0 (SPSS Inc, Chicago, US). The predictors of mortality were explored using univariate and multivariate analysis.

Results

Our study had total 330 patients of proven scrub typhus, admitted in Medicine ward between June 2012 to May 2013 in Indira Gandhi Medical College, Shimla. Only those patients who tested positive for IgM ELISA for scrub typhus were included in the study. Comparison of the baselines characteristics and complication profile of patients who survived and who died has been tabulated in Tables 1 and 2. Total mortality observed in hospital was 8.5%. The predictors of mortality were explored using univariate and multivariate analysis. Various independent predictor of mortality with significant p value (≤0.05) were duration of fever > 7 days, delay in start of treatment > 7 days, duration of hospital stay >14 days, shortness of breath, pain abdomen, altered sensorium, hypotension, tachypnea, icterus, increased leukocyte counts, thrombocytopenia, hepatic dysfunction, renal dysfunction, ARDS, septic shock, MODS and ventilatory

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Table 1: Comparison of the baseline characteristics in patients who survived and who died of scrub typhus

		Survived (302)	Death (28)	Total (330)	P-Value
Age (years)		35.86	34.75	35.76	0.64
Sex	Female	225(74.8%)	24(85.6%)	249(75.7%)	0.19
	Male	76(25.2%)	4(14.3%)	80(24.3%)	
Occupation	Housewife	213(70.5%)	22(9.4%)	235(71.2%)	
	Farmer	57(18.9%)	4(14.3%)	61(18.5%)	0.36
	Other	32(10.6%)	2(7.1%)	34(10.3%)	
Fever (days)	< 7	120(39.2%)	3(10.7%)	123(27.27%)	
	7-14	158(52.5%)	22(78.6%)	180(54.45%)	0.00
	>14	24(8.01%)	3(10.70%)	27(8.18%)	
SOB		93(30.9%)	24(85.7%)	117(35.6%)	0.00
Abdo pain		86(28.6%)	16(57.1%)	102(31.0%)	0.00
Altered sensorium		40(13.3%)	16(57.1%)	56(17.0%)	0.00
Headache		182(60.3%)	14(50.0%)	196(59.4%)	0.29
Myalgia		155(51.3%)	15(53.6%)	170(51.5%)	0.82
Tachycardia		289(95.7%)	28(100.0%)	317(96.1%)	0.54
Hypotension		103(34.6%)	22(78.6%)	125(38.6%)	0.00
RR> 24/min		107(35.4%)	27(96.4%)	134(40.6%)	0.00
Icterus		63(20.4%)	18(64.3%)	81(24.6%)	0.00
Eshcar		119(40.0%)	15(53.57%)	134(40.6%)	0.14
TLC > 11000/mm^3		93(30.9%)	19(67.1%)	112(33.97%)	0.00
Platelet <100,000/mm^3		89(28.6%)	16(57.9%)	105(31.2%)	0.00
Bilirubin>1.2 mg%		78(23.63%)	21(6.36%)	99(30%)	0.00
Total proteins <5.5 g/dl		77(25.6%)	14(50.0%)	91(27.7%)	0.03
Albumin <3.5 g/dl		149(49.5%)	18(64.3%)	168(50.8%)	0.13
SGOT		210(69.5%)	25(89.28%)	235(71.2%)	0.01
SGPT		208(68.8%)	26(92.8%)	234(70.9%)	0.00
Alkaline phosphatase		107(35.4%)	21(75%)	128(38.78%)	0.00
Creatinine		115(38.07%)	25(89.28%)	140(42.42%)	0.00
Urea		133(44.0%)	27(96.4%)	160(48.5%)	0.00

Table 2: Correlation of death with complications and delay in treatment

		Survived	Dead	Total	P value
Hepatic dysfunction		208(68.8%)	26(29.8%)	234(71.2%)	0.00
Renal dysfunction		115(38.4%)	25(89.37%)	140(42.00%)	0.00
ARDS		35(11.6%)	25(89.3%)	60(18.2%)	0.00
MODS		30(10.0%)	23(82.1%)	53(16.1%)	0.00
Septic Shock		48(15.9%)	25(89.3%)	73(22.2%)	0.00
Ventilator Support		7(2.3%)	8(28.6%)	15(4.6%)	0.00
Hospital stay (days)	<7	212(70.4%)	17(60.7%)	229(69.6%)	
	7-14	81(26.9%)	4(14.3%)	85(25.8%)	0.00
	>14	8(2.7%)	7(25.0%)	15(4.6%)	
Day of start of treatment after symptom onset	<7	142 (47.0%)	3(10.7%)	136(41.27%)	
	7-14	158(52.5%)	22(78.6%)	190(57.45%)	0.00
	>14	1(0.3%)	3(10.70%)	4(8.18%)	

support requirement. To evaluate the predictive value of the variables found to be significantly associated in univariate analysis with in hospital mortality, multivariate analysis was done keeping in hospital mortality as the dependent variable. Linear regression analysis and logistic regression analysis were used. Altered sensorium, low serum albumin, hepatic dysfunction, renal dysfunction, septic shock, MODS, ARDS, duration of fever > 7 days, day of receiving treatment > 7 days at presentation were significantly associated with high in- hospital mortality (Table 3). Only 23 patients (7%) had received anti scrub treatment (Doxycycline Or Azithromycin) prior to hospital admission. In the hospital 202(61.2%) patients received doxycycline, 120(36.36%) patients received azithromycin and 4 patients each received oxytetracycline and rifampicin. In those patients who received doxycycline, period of defervescence was 24-48 hours and those who received azithromycin period of defervescence was 48-72 hours.

Discussion

Scrub typhus has recently emerged as an important cause of mortality and morbidity among febrile patients. And very few studies so far tried to assess the severity predictors in this dreaded but potentially treatable disease. This study was carried out to assess the severity predictors from our institution which usually caters the referred cases from the peripheral units. We observed total 330 patients positive for Ig M ELISA with or without eschar out of which 250(75.80%) were females and 80(24.40%) were males. This ratio was similar in other studies from India and Korea.[7-9] In our study symptomatology and clinical finding, complications were similar to that in other studies with fever being the most common symptom present in 329 patients.[8-11] Eschar was present in 134 (40.61%) patients which was similar to 41.7%, 46% from studies done by Dass et al at Meghalaya[12] and M. Vivekanandan et al study at Pondicherry.[13] Tsay et al[14] from Taiwan and Liu et al[15] from Northern China found eschar 60% and 88.5% of patients in their studies which was quite high from present study. We found that only 23 patients had received anti scrub antibiotics (doxycycline and azithromycin) prior to hospital admission and rest other either received other antibiotics not covering scrub typhus or no treatment at all. We observed that those patients who did not receive any treatment had more rates of mortality and MODS. Those who received treatment had fewer and less severe rates of complications and mortality. Those who died in this group had received the drugs quite late in disease course. We treated the patients with doxycycline for an average of 10 days, and with azithromycin for average 7 days. We also observed that period of deference was one day less in defervescence group as compared to azithromycin group. This study showed that doxycycline is an effective drug against scrub typhus and maximum patients became afebrile within 48 hours. This is in accordance to other studies.[16,17] In our study mortality was 8.50%. Various independent predictor of mortality with significant p value ($p \leq 0.05$) were duration of fever > 7 days, delay in start of treatment > 7 days, duration of hospital stay >14 days, shortness of breath, pain abdomen, altered sensorium, hypotension,

Table 3: Correlation of in–hospital mortality with baseline characteristics

Parameter	Odds ratio	95%	C.I.	Coefficient	S.E.	Z-statistic	P-value
Sex	0.1512	0.0198	1.1532	-1.8892	1.0367	-1.8224	0.0684
SOB	2.2904	0.3173	16.5329	0.8287	1.0085	0.8218	0.4112
Abdomen pain	4.5047	0.8957	22.6538	1.5051	0.8241	1.8264	0.0678
Altered sensorium	12.2164	1.9724	75.6645	2.5028	0.9304	2.69	0.0071
Hypotension	0.16	0.0076	3.3539	-1.8324	1.5523	-1.1804	0.2378
Eschar	1.0224	0.764	1.3682	0.0222	0.1487	0.1492	0.3795
Icterus	2.6569	0.3006	23.4814	0.9772	1.1118	0.8789	0.3795
TLC	0.625	0.1732	2.2556	-0.47	0.6548	-0.7178	0.4729
S. protein	2.0373	0.4838	8.5779	0.7116	0.7335	0.9702	0.332
Albumin	0.0545	0.0057	0.5248	-2.9099	1.1557	-2.5179	0.0118
S. bilirubin	1.4653	0.4781	4.4913	0.3821	0.5715	0.6685	0.5038
Hepatic dysfunction	6.420	2.371	17.3	1.86	0.50	3.66	0.000
Renal dysfunction	15.1	4.4	51.42	2.71	0.62	4.36	0.00
Septic shock	76.05	4.1324	1399.5621	4.3314	1.486	2.9148	0.0036
MODS	7.9962	0.9517	67.1863	2.079	1.086	1.9143	0.0556
ARDS	9.7215	1.519	62.2167	2.2743	0.9471	2.4014	0.0163
Co-morbidities	0.7946	0.5583	1.131	-0.2299	0.1801	-1.2766	0.2017
Ventilatory support	0.8572	0.1265	5.8084	-0.154	0.9762	-0.1578	0.8746
Day of treatment (start)	11.55	3.3	39.66	2.44	0.62	3.84	0.00
Hospital stay	2.26	1.27	4.03	0.81	0.29	2.7	0.00

tachypnea, icterus, increased leukocyte counts, thrombocytopenia, hepatic dysfunction, renal dysfunction, ARDS, septic shock, MODS and ventilator support requirement. To evaluate the predictive value of the variables found to be significantly associated in univariate analysis with in hospital mortality, multivariate analysis was done keeping in hospital mortality as the dependent variable. Linear regression analysis and logistic regression analysis were used. Altered sensorium, low serum albumin, hepatic dysfunction, renal dysfunction, septic shock, MODS, ARDS, duration of fever > 7 days, day of receiving treatment > 7 days at presentation were significantly associated with high in- hospital mortality. Identification of these risk factors leading to fatal outcome may help physicians to start early intensive management of complicated scrub typhus. CS et al[18,19] had reported 6.1% mortality in their study. Hypotension, tachypnea, icterus, increased leukocytes counts, thrombocytopenia, hepatic dysfunction, renal dysfunction, ARDS, septic shock and MODS were independent predictor of mortality after univariate analysis. Multivariate logistic regression analysis revealed absence of eschar, event of intensive care unit admission and higher APACHE II were independent predictive variables. Kumar V et al[20] had reported 16% mortality in their study. On univariate analysis, jaundice, oliguria, elevated bilirubin, elevated SGOT, elevated SGPT, ARDS and AKI were significantly associated with mortality (p of 0.045, <0.0001, 0.005, 0.022, 0.039, 0.007 and 0.004, respectively). There was no significant association of stage of AKI with mortality (p = 0.214). On multivariate analysis, only oliguric AKI showed an independent association with mortality (p=0.002). Vikrant et al[8] had reported 16% mortality in their study. A longer hospital stay, leukocytosis, thrombocytopenia, azotemia, hypoalbuminemia, hepatic dysfunction and the complications of ARDS, encephalopathy, MOF and need for ICU supports were the factors associated with mortality. Kim et al[21] found on multivariate analysis following four factors associated with the severe complications of scrub typhus: (1) age ≥ 60 years (OR= 3.13, P = 0.002, CI = 1.53-6.41), (2) the absence of eschar (OR = 6.62, P = 0.03, CI = 1.22-35.8, (3) WBC counts > 10, 000/mm3 (OR = 3.6, P = 0.001, CI = 1.65-7.89), and (4) albumin ≤ 3.0 g/dL (OR = 5.01, P = 0.004, CI = 1.69-14.86).

Conclusion

There should be high index of suspicion in treating patients of acute febrile illness coming from endemic areas for scrub typhus. Early treatment with doxycycline should be instituted at the clinical suspicion of scrub pending investigation as it is life saving. Close follow up of the patient should be done to indentify subtle signs of organ dysfunctions to start early supportive treatment. General physician should be sensitized regarding symptoms and management of scrub typhus.

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