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An Analysis of the Clinical Manifestations and Complications of Scrub Typhus in Adult Patients

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Abstract
Background: *Rickettsial diseases are responsible for a substantial proportion of undiagnosed febrile illnesses in the tropics. Scrub Typhus is prevalent in many parts of India. It is difficult to diagnose as the symptoms and signs are often nonspecific. Untreated cases have high fatality rates if not promptly diagnosed. So awareness of the clinical manifestations of the disease will help in early diagnosis.*
Aim: *The aim of the study is to describe the clinical manifestations and complications of scrub typhus in adult patients admitted in a tertiary care hospital in Chennai.*
Materials and Methods: *This was a retrospective observational study conducted in a tertiary care hospital between January 2015 and December 2016. Adult patients admitted with history of fever and diagnosed to have scrub typhus based on positive IgM antibodies against O. tsutsugamushi were included in the study. The patients were analysed for the clinical manifestations and complications of the disease.*
Results: *A total of 50 patients were studied during this period. The duration of fever was 7 to 14 days in 37 patients (74%). The common symptoms were myalgia (66%) and cough (42%). An eschar was seen in 29 patients (58%). The common complications were thrombocytopenia (58%) and hepatitis (48%).*
Conclusion: *Scrub Typhus is one of the causes of undifferentiated fever in the tropics. The complications usually develop after the first week of the illness. A thorough search for an eschar must be made in all cases. Prompt recognition of the signs and symptoms will lead to good outcomes.*
Keywords: *Scrub typhus- Clinical manifestations and Complications – an analysis.*

Introduction

Scrub typhus is the most commonly occurring rickettsial infection in India. The disease is caused by Orientia tsutsugamushi, an obligate intracellular bacterium and transmitted through the larval mites or chiggers belonging to the family Trombiculidae. A number of small rodents, particularly wild rats of subgenus Rattus are natural hosts for scrub typhus. The disease occurs in areas where scrub vegetation is encountered and also in habitats like banks of rivers, rice fields, gardens and lawns, which can all be inhabited by chiggers. The incidence of scrub typhus is more in the rural population.

The vast variability and non specific presentation of the infection have made it difficult to diagnose clinically. Acute fever is the most common presenting symptom often associated with breathlessness, cough, nausea, vomiting, myalgia and headache.

An eschar at the site of chigger bite can be seen in early disease and is a useful diagnostic clue in scrub typhus, though its frequency varies from 7-97%. Eschars are painless ulcers up to 1 cm in size with a black necrotic centre (resembling the mark of a cigarette burn). Usually a single eschar is found on the neck, axillae, chest, abdomen and groin but multiple eschars have also been documented. Eschar on moist intertriginous surfaces (axilla, scrotum, perianal region) may be missed if not looked into carefully because they may lack the black scab and appear as shallow yellow based ulcers without surrounding hyperemia.

The complications of scrub typhus usually develop after the first week of the illness. Pneumonia, ARDS, Hepatitis, Renal failure, meningoencephalitis, myocarditis and septic shock are some of the complications of the disease.

There are various laboratory tests available for the diagnosis. Indirect Immunoperoxidase assay (IPA) and Immunofluorescence assay (IFA) are considered serological gold standard but are available in laboratories with higher levels of facilities and expertise. ELISA techniques, particularly immunoglobulin M capture assays for serum are sensitive tests for rickettsial infection and the presence of IgM antibodies indicate recent infection with rickettsial disease. A significant titre is usually found at the end of the first week and the cut off value is an optical density of 0.5. Other supportive investigations include an elevated leukocyte count, thrombocytopenia and elevated transaminases levels.

Prompt antibiotic therapy shortens the course of the disease, lowers the risk of complications and reduces morbidity and mortality due to rickettsial disease. Doxycycline is regarded as the drug of choice for the treatment of scrub typhus.

Objective

The objective of this study is to describe the clinical manifestations and complications of scrub typhus in adult patients admitted in a tertiary care centre.

Materials and Methods

The study design was a retrospective observational study conducted in a tertiary care hospital in Chennai between January 2015 and December 2016. All adult patients admitted with acute febrile illness and having positive IgM antibodies against O. tsutsugamushi were included in this study. Patients with other causes of fever were excluded. A total of 56 patients were included in the study. Two patients were excluded because of positive HbsAg status, 2 because of coexistent urinary tract infection and positive IgM for dengue infection and 2 patients left against medical advice. A total of 50 patients were studied. The study was approved by the Institutional Ethical Committee.

A detailed history, including the duration of fever, symptoms of myalgia, cough, rash, nausea and vomiting, abdominal pain, diarrhea, headache, seizures and shortness of breath were noted. The presence of any co- morbidities like Diabetes mellitus, Hypertension, Coronary artery disease, CKD and malignancy was taken into account. Hypotension was defined as a systolic blood pressure of less than 90mm of Hg .Presence of rash, rales and rhonci on auscultation, hepatomegaly, splenomegaly, lymphadenopathy, level of sensorium and signs of meningeal irritation were noted. A careful search for an eschar was made in all patients.

Laboratory investigations done included complete blood count, blood glucose, liver function tests, renal function tests, X- ray chest, ECG, ultrasound abdomen and CSF analysis in patients with suspected meningoencephalitis. Tests for malaria,

enteric fever, leptospirosis and dengue were done to exclude these diseases.

In this study thrombocytopenia (platelet count less than 1.5lakh/cu mm), hepatitis (raised transaminases levels) ARDS (tachypnea, hypoxemia and bilateral pulmonary infiltrates), shock (hypotension despite fluid resuscitation), AKI (creatinine level more than 1.5 mg/dl, a rise documented to have occured within the past 7 days) and meningoencephalitis (headache, altered sensorium, signs of meningeal irritation and consistent CSF findings) were the complications studied.

Statistical Analysis

The continuous data were expressed in terms of mean and standard deviation. The categorical data were presented by frequency and percentages. The Chi square test was used to find the association between clinical variables and complications, with Odds ratio and 95% CI.

The Statistical significance was assumed at p <0.05. The analyses were performed using SPSS statistical software (version 21.0)

Results

A total of 50 patients of scrub typhus were studied over a two year period between January 2015 and December 2016. Patients were diagnosed to have scrub typhus based on positive IgM titres. Of the 50 patients, 29 were male and 21 were female patients. Most of the patients were in the age group of 40 to 60 years. The mean age and Standard deviation was found to be 39.8±15 with minimum age 13 years and maximum age 70 years. The maximum number of admissions were in the period between September to January. Out of 50 patients, 18 had associated diseases like diabetes, hypertension and history of malignancy.

Table 1 Categorical expression of demographical parameters in the study

Parameters (n=50)	Category	Frequency (%)
Age group (years)	11—20	5 (10%)
	21—30	12 (24%)
	31—40	9 (18%)
	41—50	14 (28%)
	51—60	6 (12%)
	61—70	4 (8%)
Gender	Male	29 (58%)
	Female	21 (42%)
Month wise admissions	January	13 (26%)
	February	7 (14%)
	March	1 (2%)
	July	3 (6%)
	August	2 (4%)
	September	7 (14%)
	October	5 (10%)
	November	4 (8%)
	December	8 (16%)
Duration of fever	<7 days	3 (6%)
	7—14 days	37 (74%)
	14 days	10 (20%)
Comorbidity	Nil	32 (64%)
	DM	12 (24%)
	DM and HT	1 (2%)
	HT	4 (8%)
	Others	1 (2%)

DM- Diabetes Mallitus, HT-Hypertension

Table no. 2 and 3 show the incidence of the common symptoms and signs of the disease. All patients presented with fever, commonly associated with myalgia in 33 patients (66%). The

other common symptoms noted were cough (42%) and headache (34%). Gastrointestinal symptoms like nausea and vomiting were present in 40%, abdominal pain in 26% and diarrhea in 14%.

Table 2 Categorical expressions of symptoms of the patients in the study

Symptoms	No. of patients (%)
Myalgia	33 (66%)
Cough	21 (42%)
nausea and vomiting	20 (40%)
Headache	17 (34%)
abdominal pain	13 (26%)
Shortness of breath	11 (22%)
Diarrhea	7 (14%)
Seizures	3 (6%)

An eschar was seen in 29 out of 50 patients (58%). Hypotension was seen in 11 patients (22%). Respiratory system examination revealed the presence of rales and rhonchi in 15 patients (30%). Hepatomegaly, splenomegaly and lymphadenopathy were seen infrequently in this study. Altered sensorium was present in 5 patients and rash in 2.

Table 3. Categorical expressions of signs of the patients in the study

Signs	No of patients (%)
Rales/Rhonchi	15 (30%)
Systolic BP (< 90)	11 (22%)
Hepatomegaly	7 (14%)
Lymphadenopathy	6 (12%)
Splenomegaly	4 (8%)
Altered sensorium	5 (10%)
Maculopapular rash	2 (4%)
Eschar	29 (58%)

Investigations done revealed an elevated total count in 33 (66%) patients. Platelet count was reduced to less than 1.5 lakhs in 29 patients. The liver enzymes AST and ALT were elevated in 24 patients. Serum creatinine levels were elevated to more than 1.5 mg/dl in 6 patients who did not have history of previous renal disease. X- ray chest showed the presence of bilateral diffuse infiltrates in 7 patients and other abnormalities like pleural effusion and unilateral opacities in 4 patients. Ultrasonogram showed abnormal findings like hepatomegaly, splenomegaly and ascites in 9 patients. One patient had a splenic abscess. ECG abnormalities seen were sinus tachycardia, occasional ventricular ectopics and RBBB in 5 patients.

Complications were seen in 38 (76%) out of the 50 patients. The most common complications were thrombocytopenia and hepatitis. Most of the complications were seen in combination in a given patient. Oxygen saturation was reduced in 5 patients with tachypnea and bilateral diffuse lung opacities. Headache, altered sensorium and signs of meningeal irritation were seen in 5 patients. Lumbar puncture and CSF analysis was done in 4 patients. It showed elevated protein in the range of 60 to 100 mg/dl with increased cells, predominantly lymphocytes in 3 patients and elevated protein alone in 1. 11 patients had hypotension, out of which 3 patients needed both fluids and inotropic support. GI bleed in 2 patients and quadriparesis in 1 were some of the rare complications noted. There was one death due to ARDS and shock. Table no. 4 shows the incidence of complications noted in this study.

Table 4 Categorical expressions of complications of the patients in the study

Complications	No. of patients (%)
Hepatitis	5 (10%)
Hepatitis and Thrombocytopenia	11 (22%)
Hepatitis,Thrombocytopenia,ARDS	1 (2%)
Hepatitis,Thrombocytopenia,ARDS, AKI	1 (2%)
Hepatitis,Thrombocytopenia,ARDS,AKI,Shock	1 (2%)
Hepatitis,Thrombocytopenia, AKI	2 (4%)
Hepatitis,Thrombocytopenia,Meningoencephalitis	1 (2%)
Hepatitis,Thrombocytopenia,Others	1 (2%)
Hepatitis,AKI,Others	1 (2%)
Thrombocytopenia	7 (14%)
Thrombocytopenia,ARDS	1 (2%)
Thrombocytopenia,ARDS,AKI,Shock	1 (2%)
Thrombocytopenia,Meningoencephalitis,shock	1 (2%)
Thrombocytopenia, Others	1 (2%)
Meningoencephalitis	2 (4%)
Others	1 (2%)
Nil	12 (24%)

The association between co- morbidities like diabetes and hypertension and the presence of complications were studied with a view to analyze whether underlying diseases were related to the severity of scrub typhus.

Table 5 Relation between Co-morbidity and complications in adult patients with scrub typhus

Co-morbidity	Complications			Pearson Chi-Square		Odds Ratio (95% CI)
	Yes	No	Total	Test value, df	p value	
Yes	12 (67%)	6 (33%)	18 (100%)	1.343, 1	0.246 (NS)	0.46 (0.12--1.73)
No	26 (81%)	6 (19%)	32 (100%)			
Total	38 (76%)	12(24%)	50(100%)			

NS- Not Significant.

Though, there was no statistically significant (p=0.246) association between comorbidity and complications, it was noticeable that, out of 50 patients, 12(24%) patients had both co-morbidity and complications. And the risk was estimated up to 1.73 times (OR = 0.46, 95%CI= 0.12- 1.73).

The incidence of an eschar is a highly variable finding and in this study, it was present in 29 out of 50 patients. The relation between eschar and complications is shown in table 6.

Table 6. Relation between Eschar and complications in adult patients with scrub typhus

Eschar	Complications			Pearson Chi-Square		Odds Ratio (95% CI)
	Yes	No	Total	Test value, df	p value	
Yes	20 (69%)	9 (31%)	29 (100%)	1.873, 1	0.171 (NS)	0.37 (0.09--1.59)
No	18 (86%)	3 (14%)	21 (100%)			
Total	38 (76%)	12 (24%)	50(100%)			

NS- Not Significant

There was no statistically significant (p=0.171) association between Eschar and complications But it is important to note that, out of 50 patients, 20 (40%) patients had both Eschar and complications. And the risk was estimated up to 1.59 times (OR = 0.37, 95% CI= 0.09—1.59)

Discussion

Scrub typhus is prevalent in many parts of India. It is difficult to diagnose because the symptoms and signs are often non-specific. This study was done to analyse the clinical manifestations and complications of scrub typhus in adult patients. The study was a retrospective study conducted on patients admitted with scrub typhus during a two year period between January 2015 and December 2016 in a tertiary care hospital in Chennai. Patients admitted with history of fever and IgM ELISA confirmed scrub typhus were included in this study. Patients with other causes of fever were excluded.

All patients in this study were admitted with a history of fever. The duration of fever was more than seven days in the majority of cases (74%). Patients admitted to our hospital are usually referred from other institutions after the first week of illness and this is also the period when the complications of scrub typhus occur. Most of the patients were admitted during the months of September to January. The period of the epidemic is influenced by the activities of the infected mite. It occurs more frequently during the rainy season.[1]

The clinical spectrum of scrub typhus is broad with most infections being of mild to moderate severity. The eschar is the single most important clue to diagnose a suspect case of scrub typhus. The incidence of the eschar varies from 7 to 97%.[2]In our study, the incidence was 58%, which is higher than that seen in a similar study by M.V. S. Subbalakshmi et al in which the incidence of an eschar was 13%.[3]The high incidence in our study is probably because IgM was sent in most of our patients after the eschar was detected.

Symptoms usually begin six to ten days after the mite bite. The typical features are usually fever, generalised or systemic lymphadenopathy, a macular or maculopapular rash, severe headache and myalgia. Muscle tenderness is minimal or absent. Nausea and vomiting, diarrhea, constipation, conjunctival suffusion and reversible sensorineural deafness can also occur. In our study also, the most common symptom was myalgia, followed by cough, nausea and vomiting.[4] A rash was seen in only 2% of patients in this study. This has been reported in other studies also.[2]

Hypotension was seen in 11 patients, out of which 8 patients improved with fluids alone. Regional lymphadenopathy is commonly observed. But the incidence in our study was only 12%. Hepatomegaly and splenomegaly was seen infrequently with an incidence of 14% and 8% respectively. This was in contrast to the study conducted by M.Vivekanandan et al where the incidence of hepatomegaly and splenomegaly was 28% and 20%.[5]

Supportive laboratory investigations provide additional diagnostic clues and can also indicate the severity and development of complications. Total leukocyte count may be normal early but later in the course of the disease, leukocytosis occurs. Thrombocytopenia is seen in a majority of patients. Raised transaminases levels are commonly observed. A clinical algorithm has been proposed for diagnosis of scrub typhus among patients hospitalized with febrile illness. If a combination of elevated transaminases, thrombocytopenia and leukocytosis is used, the specificity and positive predictive value for diagnosis of scrub typhus is above 80%.[6]In our study, leukocytosis was seen in 66% of patients and thrombocytopenia in 58% .Elevation of liver transaminases levels was seen with an incidence of 48%. Similar abnormalities have been seen in other studies also.

The complications of scrub typhus are known to occur after the first week of the illness. Jaundice, renal failure, pneumonia, ARDS, septic shock, meningoencephalitis and myocarditis are some of the complications associated with this disease. In

this study, thrombocytopenia was the most common complication noted. Hepatitis was also common with an incidence of 48%. Renal failure, ARDS, Meningoencephalitis and shock were seen with less frequency. One patient with ARDS and shock died during the course of illness.

Eschar is a common finding in scrub typhus but its positive association with disease severity has not been established. In this study eschar positive (58%) patients were compared with eschar negative (42%) patients to see if the occurrence of complications was different in both groups. The incidence of complications was 53% in the eschar positive group and 47% in the eschar negative group, which was not statistically significant (p=0.171). This finding was similar to other studies where the presence of an eschar did not have a statistical significant impact on mortality.[4, 8] This is in conflict with studies which showed that the presence of an eschar was associated with severe infection.[9.] It is important to note that in this study, 20(69%) patients out of total eschar cases (29) had both eschar and complications. Due to such conflicting evidence and small sample size which was a limitation in this study, it is difficult to estabilish an eschar as a clear prognostic indicator. This is an area for further research.

The presence of pre- existing medical conditions like diabetes and hypertension did not have any statistical significant association with the complications of scrub typhus.[4] It is possible that the sample size was inadequate to prove this significance.

One patient, a 26 year old female presented with fever of two weeks duration, dyspnea and chest pain. An eschar was noted in the anterior abdominal wall near the umbilicus and IgM for scrub typhus was positive. Tests for dengue, leptospirosis, enteric fever and malaria were negative. Serology for Hepatitis B, C and HIV were negative. She developed a flaccid quadriparesis, probably Polyneuropathy. Nerve conduction study however was not done as the weakness improved. She also had multiple organ involvement with hepatitis, renal failure and thrombocytopenia. She improved with antibiotics and other supportive measures.

In the clinical setting, a diagnosis of scrub typhus is considered when a patient with an acute febrile illness has an eschar and a positive IgM ELISA for scrub typhus and other causes for fever excluded. In the absence of an eschar, a positive IgM ELISA in the appropriate clinical setting with defervescence within 48 hours of starting doxycycline with other etiologies ruled out also suggests scrub typhus infection[7]. In our study all patients with fever and positive IgM titre were included, after ruling out other causes of undifferentiated fevers like malaria, dengue, leptospirosis and enteric fever.

Treatment of scrub typhus must be initiated early in the course of the disease, based on a presumptive diagnosis, to reduce mortality and morbidity.[1]Doxycycline is the drug of choice. The recommended treatment duration is 7-14 days. The alternative drugs are Azithromycin and Chloramphenicol. Rifampicin has also been used as an alternative drug. Antibiotic therapy brings about prompt disappearance of the fever and dramatic clinical improvement. Rapid defervesce-ence after antibiotic treatment is so characteristic that it is used as a diagnostic test for O. tsutsugamushi infection.[1] Supportive management is necessary in the management of complications.

Conclusion

Scrub typhus is an important differential diagnosis of undifferentiated fever in our country. With appropriate antibiotic treatment, mortality is rare and the recovery period is short and usually without complications. The eschar is the most important diagnostic clue in patients with scrub typhus and should be thoroughly searched for especially in covered areas such as the groin, genitalia, inframammary area and axilla. Serological tests for scrub typhus must be done in patients suffering from acute undifferentiated fever. With increased awareness, early diagnosis and appropriate treatment, the morbidity and mortality of the disease can be prevented.

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