

Original Research Article

Cardiovascular abnormalities in severe scrub typhus

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ABSTRACT

Background: Himachal Pradesh is an endemic area for scrub typhus. If not treated early, it can lead to life threatening complications, affecting various systems of the body. Hence, this study was done with an objective to study the cardiovascular abnormalities in patients of severe scrub typhus.

Methods: Authors conducted a hospital-based study in Departments of Medicine and Cardiology, of a tertiary care hospital in Sub-himalayan region in patients of severe scrub typhus from June 2016 to May 2017.

Results: Thirty-two (55%) patients were aged <60 years with female preponderance (72%). Electrocardiographic changes included sinus tachycardia in 56 (97%), axis deviation in 5(9%), ST-T changes in 3(5%) and atrial fibrillation in 1(2%). Echocardiographic changes included tricuspid regurgitation in 14(24%), pericardial effusion in 4(7%), myocarditis in 1(2%) and Regional wall motion abnormality in 1(2%). Left ventricular ejection fraction >45% in 47 (81%) and <45% in 11(19%). Fifty-one patients had hypotension at presentation and 49 (90%) of them improved. Interestingly, 10 of 11 patients with reduced EF (<45%) survived whereas 6 of total 7 patients, who died, had preserved EF (>45 %).

Conclusions: Severe scrub typhus manifested with ST/T changes, myocarditis, pericardial effusion, arrhythmias, shock and patients with reduced EF on Echocardiography had better outcome.

Keywords: Echocardiographic changes, Electrocardiographic changes, Scrub typhus, Severity

INTRODUCTION

Scrub typhus, an acute febrile illness of variable severity is caused by *Orientia tsutsugamushi*. An arthropod vector of the *Trombiculidae* family transmits it to humans.¹

It has been estimated that about one billion people are at risk of acquiring scrub typhus and annual burden of one million cases has been estimated. Mortality rates in untreated patients have been estimated up to 30%.²

The skin site of inoculation of *Orientia tsutsugamushi* becomes necrotic and evolves into a painless lesion called

eschar. The endothelial cells of vascular lining of various organs are the site of proliferation of *Orientia*. The bacteria attack brain, pancreas, lung, kidney and skin releasing inflammatory mediators like cytokines, prostaglandins, and leukotrienes.³In a autopsy based study conducted by Levine *et al* on patients of scrub typhus reported myocardial involvement in 80% patients and histopathological perivasculitis was the characteristic of scrub typhus. The injury to cardiac myocytes, vasculitis and perivasculitis in the myocardium leading to cellular infiltration along with haemorrhage and oedema of interstitial tissues has been reported.⁴Yotsakura *et al* reported a case of scrub typhus with myocarditis where

Rickettsia tsutsugamushi was demonstrated on endomyocardial biopsy.⁵Chang *et al* reported pericarditis in a patient of scrub typhus.⁶Karthik *et al* reported mild to moderate pericardial effusion in 51% and myocarditis in 12% patients of scrub typhus.⁷

METHODS

This hospital-based study was carried out in Departments of Medicine and Cardiology, of a tertiary care hospital in Sub-himalayan region in patients of severe scrub typhus from June 2016 to May 2017.

The patients of fever with rash and/or eschar with IgM antibodies on ELISA(InBios International, Inc, Seattle, USA) to *O. tsutsugamushi* were diagnosed as scrub typhus. All patients were treated empirically with drugs effective in rickettsial diseases i.e. doxycycline and/or azithromycin. The study was approved by the Institutional Ethics Committee. Operational Definitions are as per Table 1.⁸

Table 1: Main Clinical Features at Presentation (n=58).

Clinical Features	Frequency (%)
Symptoms	
Fever	58 (100%)
Headache	49 (85%)
Vomiting	46 (79%)
Myalgia	39 (67%)
Shortness of breath	34 (59%)
Cough	25 (43%)
Chills and rigors	20 (35%)
Loose stool	10 (17%)
Altered Sensorium	4 (7%)
Seizure	2 (3%)
Abdominal Pain	1 (2%)
Signs	
Tachycardia (>90/min)	56 (97%)
Hypotension	51 (88%)
Temperature(>102°F)	44 (76%)
Icterus	15 (26%)
Skin Rash	15 (26%)
Eschar	15 (26%)

Scrub typhus

A patient with clinical features suggestive of scrub typhus (fever, rash, eschar etc.) and positive IgM antibodies by ELISA.

Severe Scrub typhus

A case of scrub typhus fulfilling criteria of severe sepsis or septic shock or evidence of organ system failure.

Sepsis was defined as at least two of the following signs and symptoms (SIRS) that are both present and new to the patient and suspicion of new infection.

- Hyperthermia >38.3°C or Hypothermia <36°C
- Tachycardia >90 bpm
- Leukocytosis (>12,000 µL⁻¹) or Leukopenia (<4,000 µL⁻¹) or >10% bands
- Acutely Altered Mental Status
- Tachypnea >20/min
- Hyperglycemia (>120 mg/dl) in the absence of diabetes.

Severe sepsis includes SIRS and at least one of the following signs of hypo perfusion or organ dysfunction that is new and not explained by other known aetiology of organ dysfunction.

- Cardiovascular: Arterial systolic blood pressure ≤90 mm of Hg or mean arterial pressure ≤70 mm of Hg that responds to administration of IV fluids
- Renal: Urine Output <0.5 ml/kg/hr for 1 hr despite adequate fluid resuscitation.
- Respiratory: Pao₂/Fio₂ ≤250 or, if lung is only dysfunctional organ ≤200.
- Haematological: Platelet count <80000µl or 50% decrease in platelet count from highest value recorded over previous 3 days.
- Unexplained metabolic acidosis: A pH ≤7.30 or a base deficit ≥5.0 mEq/L and plasma lactate level >1.5 times upper limit of reporting lab.
- Hepatic dysfunction as evidenced by Bilirubin >2 or INR >1.5.

Septic shock Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 h despite adequate fluid resuscitation; Or Need for vasopressors to maintain systolic blood pressure 90 mmHg or mean arterial pressure 70 mmHg.

Refractory septic shock Septic shock that lasts for >1 h and does not respond to fluid or pressor administration.⁸

*Multiple-organ dysfunction syndrome (MODS)*⁹- Dysfunction of >1 one organ, requiring intervention to maintain homeostasis.

1. A relevant history was recorded.
2. 12 lead ECG was used to record: Heart Rate, Axis, Rhythm, ST changes, T wave changes, Arrhythmias, Bundle Branch Blocks and Ischemia.
3. Echocardiography: Was done using i33 ECHO machine with 2-5 Broadband phase Array probe of Philips Medical System to record-LV volumes, LV mass, Global LV Systolic function, RWMA, I.V.C diameter.

Reference Limits and Partition Values⁶

LV Ejection Fraction (%) was defined as Mild LV systolic dysfunction (45-54%), Moderate LV systolic dysfunction (30-44%) and Severe LV systolic dysfunction (<30%).

LV Mass / BSA (g/m)² was defined as in normal male it 49-115 and female 43-95 and mild LVH 116 -131 nd female 96 -108.

Inclusion Criteria

- Patients features consistent with scrub typhus, showing IgM antibodies by ELISA
- Age >18 years.

Exclusion Criteria

- Patients who died within 12 hours of hospitalization.
- Patients with history of any cardiac disease.

All patients with features consistent with scrub typhus showing IgM antibodies by ELISA were included in study. The relevant history was recorded in a performa. The haematological and biochemical investigations were performed at the time of admission to hospital. A 12 lead ECG was done and Echocardiography was performed using i33 ECHO machine with 2-5 Broadband phase Array probe of Philips Medical System. Echocardiography was repeated 3 months after discharge from hospital.

Left Ventricular Systolic dysfunction was defined as LV Ejection Fraction(LVEF) 45-54% was defined as Mild LV systolic dysfunction, 30-44% as Moderate LV systolic dysfunction and LVEF <30% as Severe LV systolic dysfunction. Left Ventricular Mass/ BSA of 116-131 (g/m)² in males and 96-108 (g/m)² in females was defined as Left Ventricular Hypertrophy.⁹ The data was entered on Microsoft Excel spreadsheet and descriptive analysis for baseline characteristics of patients. Cross tabulation with outcome variable of interest was done using statistical SPSS software version 22.0.0.0 and Epi Info 7.1.5 for windows.

RESULTS

Of total 58 patients 32 (55%) were aged <60 years. Highest number, 31 % of patients were in the age group of 41-50 and 42 (72%) were females. On details analysis of clinical features, fever (100%), headache (85%), vomiting (79%), myalgia (67%) and shortness of breath (59%) were main symptoms. On examination, 56 (97%) patients had tachycardia and 51 (88%) patients were in hypotension. Icterus (26%), skin rash (26%) and eschar (26%) were other clinical signs noted (Table 1). On systemic examination, tachycardia (79%) and basal crepitations in chest (52%) were main clinical findings noted (Table 2).

On examination of cardiovascular system, 46 (79%) patients had tachycardia at time of examination, 5(9%) had other added sound i.e. short systolic murmur at apex (Grade II/VI) in 2(3%) and pan systolic murmur in tricuspid area in 3(5%) patients.

Table 2: Findings on Systemic Examination (n=58).

System Findings	Frequency (%)
Cardiovascular System	
Tachycardia	46 (79%)
Other added sounds	5 (9%)
Respiratory System	
Crepts	30 (52%)
Abdomen	
Tender epigastrium	6 (10%)
Splenomegaly	4 (7%)
Hepatomegaly	3 (5%)
Central Nervous System	
Altered sensorium	1 (2%)
Cerebellar signs	1 (2%)

On ECG, tachycardia was consistent finding in majority of severe scrub typhus patients (97%). Left axis deviation was present in 4(7%) and right axis deviation in only 1 (2%). PR interval was decreased in 7(12%) and ST/T changes i.e. depression/inversion was present in 3(5%).

Table 3: Laboratory Abnormalities in study group(n=58).

Investigation	Frequency (%)
Hematological	
Thrombocytopenia (<150.0thou/μl)	54(93%)
Leucocytosis (>12.0 thou/μl)	45(78%)
Leucopenia (< 4.0 thou/μl)	3(5%)
Biochemistry	
Transaminitis (SGOT/SGPT >100 IU/ml)	55(95%)
Hypoalbuminemia (<3.5g/dl)	45(78%)
Serum Urea (>40mg/dl)	44(76%)
Hyperbilirubinemia (>2g/dl)	36(63%)
Serum Creatinine (>1.5 mg/dl)	35(60%)
Random Blood Sugar (>200 mg/dl)	4 (7%)

On analysis of laboratory abnormalities in the study group (Table 3), thrombocytopenia (95%) and leucocytosis (78%) were main haematological abnormalities. In biochemical investigations of serum, transaminitis ((95%), hypoalbuminemia (78%), hyperbilirubinemia (63%) and raised serum creatinine (60%) were noted.

On 2D ECHO, 14(24%) had evidence of tricuspid regurgitation (TR), 11 patients of them showed features of Pulmonary Artery Hypertension (PAH) with tricuspid regurgitation, mild LVH in 8(14%), 4 (7%) had pericardial

effusion, RWMA was noted in 1 patients and mild LVH in 8(14%) and only 1 patient had myocarditis. LVEF (Left ventricular ejection fraction) was >45% in 47 patients and remaining 11 had EF <45%. LVEF was 30-44% in 9(16%) and LVEF <30% in 2(3%) and IVC diameter <1.5 cm was seen in 20(34%). Of total 11 patients with EF <45%, 10 survived. Main cardiovascular abnormalities noted in the study group are given in Table 4.

Table 4: Main Cardiovascular Abnormalities in study group (n=58).

Finding	Frequency (%)
Electrocardiography	
Heart Rate	
> 90/min	56 (97%)
< 90/min	2 (3%)
Left Axis Deviation	4 (7%)
Right Axis Deviation	1(2%)
Atrial Fibrillation	1 (2%)
Decreased PR Interval	7 (12%)
ST/T Wave	3 (3%)
Depression/ Inversion	
Echocardiography	
LVEF	
>45%	47 (81%)
30-44%	9 (16%)
< 30%	2 (3%)
Tricuspid Regurgitation	14 (24%)
Mild LVH	8 (14%)
Pericardial Effusion	4 (7%)
RWMA	1(2%)
Myocarditis	1(2%)

On repeat 2D ECHO after 3 months, pericardial effusion disappeared in all 4 patients. Of total 14 patients with TR, in 7 patients TR disappeared, while there was evidence of mild TR in 1 patient, 2 patients with TR died and remaining 4 patients were lost to follow up.

All patients received anti-rickettsial antibiotics in form of doxycycline, and/or azithromycin (IV, oral). Fifty-one(88%) patients had hypotension, of which 38(75%) were treated with IV fluids and in remaining 13(25%) inotropic agents were also used. Of total 51 patients with hypotension, 46(90%) improved after treatment.

Total 7 (12%) out of 58 patients of severe scrub typhus patients died. Of total 7 patients who died, 6 had LVEF >45%, whereas death occurred in 1 patient with LVEF 27%. Four of these 7 patients, who died, had hypotension unresponsive to ionotropes.

DISCUSSION

The age of study participants ranged from 18 to 80 years. Twenty six (45%) patients in our study were in aged <40 years. The higher incidence in younger and active age

group with female preponderance (72%) in the study group has previously been reported.^{10, 11}

The various clinical features present in study group corroborate with most other studies. The presence of eschar was less frequent in our study as compared to other studies. This may be due to reason that eschar is seen less frequently in South Asians.^{12, 13}

In our study leucocytosis was present in 45 (78%), leucopenia in 3(5%) and thrombocytopenia in 54(93%) patients. Leucocytosis in 30% and leucopenia in 2%.¹⁴ However leucocytosis in 44% and thrombocytopenia in 62% of patients.¹⁵ The higher incidence of hyperbilirubinemia, transaminitis, hypoalbuminemia and renal dysfunction in our study can be due to the fact that all patients included were suffering of severe scrub typhus.

In our study on electrocardiography abnormalities included sinus tachycardia in 56(97%), axis deviation in 5(9%), ST-T changes in 3(5%), atrial fibrillation in 1(2%). Cases of scrub typhus with ECG changes like low voltage, ST- T changes, wide QRS, PVC's and VT.¹⁶

A 42 year old male suffering from scrub typhus with ST elevation in V1-V6 region on electrocardiography.¹⁷ On electrocardiography ST elevation I, aVL leads and in leads V2, V3 along with symmetric T inversion in V2-V6 were documented also.¹⁸ Their study showed ST changes on ECG in myocarditis and paroxysmal AF. In our study 3 patients had ST changes and 1 had AF.¹⁹

In a study of 29 adult patients of scrub typhus in Northern Thailand, the ECG manifestations of scrub typhus were prospectively evaluated. Twenty two (76%) patients did not show any abnormality on ECG whereas 7 patients showed ST segment/T wave changes (10%), U waves (7%), and premature ventricular beats (4%).²⁰ Conducted a study of ECG changes in 98 patients of scrub typhus. During febrile stage sinus arrhythmia with some beats below 60 per minute, sinus tachycardia, first degree A-V block, Q-Tc interval prolongation, incomplete RBBB, AV junctional escapes and right axis deviation were noted. ST segment elevation in V2 tall and peaked T waves in V2-4, low voltage of flat T waves in left precordial leads, T wave inversion in V3-4, notched T waves in V3 were also documented. These ECG abnormalities were common during the acute illness phase and prompt treatment with antibiotics prevented the serious cardiac complications.²¹

Echocardiographic changes in our study included tricuspid regurgitation (TR) with and without pulmonary hypertension (PAH) in 14(24%), RWMA in 1(2%) and myocarditis in 1(2%). In study of 91 patients of complicated scrub typhus, myocarditis was found in 14%.²² Occurrence of pericarditis on autopsy in 58% patients of scrub typhus. The cardiac complications occurred in 5-25% which included hypotension due to

shock, arrhythmias, myocarditis and pericardial effusion.²³ In this study 4 patients had pericardial effusion which disappeared in all patients on repeat Echocardiography. Pericardial effusion in patient of Tsutsugamushi infection and reported mild to moderate pericardial effusion in 51% but none had cardiac tamponade.⁶ They also reported myocarditis in 12% patients, but it was not associated increased mortality. They concluded that cardiac involvement in patients of scrub typhus was associated with increased morbidity.⁷ A study reported left ventricle and left atrial dysfunction with decreased ejection fraction and acute fulminant myocarditis with no prior cardiomyopathies on Echocardiography in patients of scrub typhus.¹⁶

A prospective study was conducted on 51 septic shock patients in Thailand, and scrub typhus was documented in 18 (35%) patients.²³ In present study 51 (88%) of total 58 patients had hypotension at presentation and 46 (90%) of them improved and 7 died. In 38 (75%) patients, hypotension responded to only intravenous fluids whereas remaining 13 required additional ionotropes. Five of 13 patients were unresponsive to fluids with ionotropes and in remaining 8 patients' blood pressure improved. Of total 7 patients who died, 6 had EF >45%, whereas in remaining 1 patient EF was 27%.

On screening English Language Literature, no study was available on relationship of LV Ejection Fraction on Echocardiography and outcome of patients suffering from scrub typhus. However present literature on effects of sepsis caused due to non-scrub typhus diseases suggest that the mortality increased significantly (70-90%) when sepsis was accompanied with cardiovascular dysfunction in comparison to patients of sepsis without cardiovascular impairment (20 %).^{24,25}

The septic shock was associated with significant myocardial dysfunction despite increased cardiac output and a normal stroke volume. The end-diastolic volume was higher and EF was lower in survivors when compared to non-survivors of septic shock.²⁶ Studied 90 patients of septic shock during later phase of septic shock and concluded that the cardiac function and EF abnormalities were fully reversible after 7 to 10 days of the onset of sepsis.²⁷ These findings are in agreement with our study where 11 patients had EF <45%, 10 of them survived and 6 of 7 patients with EF >45% died.

In this study total 14 patients had TR and 11 of them had associated PAH also. Only 8 patients reported for repeat Echocardiography at 3 months and TR disappeared in 7 patients. Reported that Scrub typhus is frequently associated with interstitial pneumonia (IP) and its presence was closely associated with the disease severity of scrub typhus.²⁸ The presence of IP is associated with hypoxia, hypotension, severe thrombocytopenia, hypoalbuminemia, cardiomegaly and pulmonary alveolar edema. In this study of severe scrub typhus, the presence of IP could have been responsible for TR which

disappeared subsequently. Vieillard-Baron A reported that the right ventricle is especially overloaded in ARDS.²⁹

CONCLUSION

Severe scrub typhus can manifest with potentially life-threatening cardiovascular complications likes ST/T changes, myocarditis, pericardial effusion, arrhythmias, valvular involvement and shock. The majority of patients with septic shock respond to antibiotics and fluid resuscitation however a few may require additional support of inotropic agents also. The patients of severe scrub typhus with reduced EF on Echocardiography had better outcome.

This is an observational study of patients was conducted on a small sample size. By virtue of the single-center study design, the results may not be generalized to other however an interesting relationship of association of EF on Echocardiography and outcome of patients suffering from severe scrub typhus emerged from this study and this study sets the stage for further randomized control trials encompassing a greater sample size to help better elucidate and confirm our findings.

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