Article

Scrub typhus: an unrecognized threat in South India – clinical profile and predictors of mortality

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TROPICAL DOCTOR 2010; **40**: 129–133
DOI: 10.1258/td.2010.090452

SUMMARY Scrub typhus is an important cause of acute undifferentiated febrile illnesses in the Indian subcontinent. Delay in diagnosis and in the initiation of appropriate treatment can result in severe complications such as acute respiratory distress syndrome (ARDS), septic shock and multisystem organ failure culminating in death. We conducted a prospective, observational study to delineate the clinical profile and predictors of mortality in scrub typhus in adults admitted to the medical wards of a tertiary care, referral hospital in South India over a one-year period. The case fatality rate in this study was 12.2%. Metabolic acidosis (odds ratio [OR] 6.1), ARDS (OR 3.6), altered sensorium (OR 3.6) and shock (OR 3.1) were independent predictors of mortality. It appears that scrub typhus has four possible overlapping clinical presentations: mild disease; respiratory predominant disease; central nervous system predominant disease (meningoencephalitis); or sepsis syndrome. Given the telltale presence of an eschar (evident in 45.5%), the characteristic clinical profile and the dramatic therapeutic response to a cheap, yet effective, drug such as doxycycline, medical practitioners in the region should have ample opportunity to reach an early diagnosis and initiate treatment which could, potentially, reduce the mortality and morbidity associated with scrub typhus.

Introduction

Orientia tsutsugamushi, the causative organism of scrub typhus, is a Gram-negative, obligate intracellular parasite that survives in both vertebrate and arthropod hosts.[1] The organism is transmitted to vertebrates through the bite of the larval form (chigger) of the trombiculid mite. Scrub typhus is an acute febrile illness that results in significant morbidity and mortality in the Asia-Pacific region. It is also identified as a cause of acute febrile illnesses in returning travellers in the West. DNA and immunological strain analysis suggest that the Karp strain and its related strains are most common in endemic regions, including South Asia.[2] Other strains such as the Gilliam, Kato, Shimokoshi, Kawasaki, Kuroki and others have been described. Tamura *et al.* have described the differences in virulence between the antigenic variants among mice.[1]

The predominant pathology in scrub typhus is that of focal, or disseminated vasculitis, which occurs as a result of the destruction of endothelial cells and perivascular infiltration of leukocytes. This, in turn, results in protean manifestations ranging from a self-limiting febrile illness to a fulminant sepsis-syndrome with multisystem organ failure. The severity of the disease depends on the virulence of the strain, the susceptibility of the host, or both.

Reports have suggested that scrub typhus is endemic in the Asia-Pacific region with sporadic outbreaks occurring within the Indian subcontinent.[3–10] In India, scrub typhus has been reported from Tamil Nadu, Kerala, Maharashtra, Himachal Pradesh and Bihar.[10] However, the disease burden and clinical profile has not been fully understood in this region. Prompt diagnosis and treatment can significantly reduce morbidity, mortality and the cost of care associated with the disease. Hence, this study was conducted in order to delineate the clinical profile and predictors of mortality in a cohort of patients with scrub typhus in South India.

Methodology

This study is a sub-analysis of a prospective, observational study conducted in order to delineate the aetiology of acute undifferentiated febrile illnesses (AFI) admitted to the medical wards of a tertiary care referral hospital (Christian Medical College, Vellore) in South India over a one-year period (January 2007–January 2008). The study was approved by the institutional review board of the hospital.

Patients aged 16 years and above, who presented with a febrile illness of 5 to 21 days' duration (temperature documented in the hospital as $>101^{o}$F), with no evident focus of infection after the initial clinical evaluation and baseline investigations (including a chest X-ray and urine microscopy), were included in the study after informed written consent had been given. Patients were excluded if they were immunocompromised (HIV-positive, on immunosuppressants or had

haematological or autoimmune diseases). At admission, all included patients were tested for scrub typhus using an IgM enzyme-linked immunosorbent assay (ELISA) (Pan Bio Ltd, Brisbane, Australia; value $\geq$16 units was considered as positive). Convalescent sera were collected 2–4 weeks after discharge and the test was repeated as required. Additional tests conducted on all patients were: two blood cultures; three thin smears for malarial parasites; serology for dengue (IgM, IgG) rapid device; leptospira (IgM) ELISA; hantavirus (IgM, IgG) qualitative assay; typhidot (IgM, IgG); and spotted fever IgM ELISA (in cases with rash). The diagnosis of scrub typhus was made based on the following criteria:

(1) AFI and the presence of a positive eschar and scrub IgM ELISA, or;
(2) AFI plus a positive scrub IgM ELISA plus defervesence within 48 h of the initiation of doxycycline, or;
(3) AFI plus scrub IgM ELISA seroconversion on convalescent sera, or;
(4) AFI plus a positive scrub IgM ELISA with other serologies negative.

Clinical criteria were not included in the diagnostic criteria, in order to allow for clinical comparisons between each of the causes of AFI.

Results

Three hundred and ninety-eight patients were admitted with an AFI over a one-year period and 189 (47.5%) were diagnosed with scrub typhus. The majority of patients were from the districts of Chitoor, Andhra Pradesh (23.8%) and Vellore, Tamil Nadu (56.6%) in South India. Sporadic cases occurred throughout the year with an escalation of cases during the cooler months of August through January (the peak seemed to be during September with 24.9% of the cases occurring in that month). The mean age was 45.4 (17.2) years and 100 (52.9%) were males. The patients essentially belonged to the unemployed/housewife (42.9%) and unskilled labourer/farmer (38.8%) occupational categories. The mean duration of the fever at presentation was 9.5 (3.5) days. The mean duration of hospital stay was 5.5 (4.6) days. The case fatality rate was 12.2% (23 deaths).

The clinical profile is presented in Table 1. The primary symptoms on presentation were headache, vomiting and myalgias, cough and breathlessness, altered sensorium, abdominal pain and loose stools. The predominant signs were tachypnea, tachycardia, hepatomegaly, crepitations, altered sensorium and neck stiffness. An eschar was evident in 45.5% and rash in 5.8% of patients; 13.8% of the patients presented with shock; leucocytosis ($>$11500 cells/mm^3) was seen in 37%; thrombocytopenia ($<$150,000 cells/mm^3) was present in 70.7% of patients; and severe thrombocytopenia ($<$50,000 cells/mm^3) was evident in 27%. Muscle injury, exhibited through elevated creatinine phosphokinase, was evident especially in patients who died, although this was not statistically significant. Serum hepatic transaminases were elevated in the majority of patients (95.2% had aspartate aminotransferase [AST] $>$ 45U/L). However, 70.9% had only mild transaminase elevation (serum AST between 45–200U/L). Acute respiratory distress syndrome (ARDS) was evident in 24.9% and aseptic meningitis in 20.6% of the patients.

On univariate analysis, a history of breathlessness, altered sensorium, oliguria, rash and overt bleeding manifestations, clinical examination revealing tachycardia, tachypnea, shock, respiratory crepitations and altered sensorium were predictors of mortality. Univariate analysis for investigations indicated that leucocytosis, immature white blood cells, elevated creatinine, metabolic acidosis, elevated AST, hypoalbuminaemia, hypoxia and ARDS were predictors of mortality. On multivariate analysis (Table 2), metabolic acidosis, ARDS, altered sensorium, shock and renal failure were independent predictors of mortality.

Discussion

Delay in diagnosis of scrub typhus and initiation of appropriate treatment can result in severe complications such as ARDS, shock, acute kidney failure, hepatic dysfunction, myocarditis, disseminated intravascular coagulation and multisystem organ failure culminating in death.[11–13] Although serological tests, including immunofluorescent assays, ELISA and polymerase chain reaction have been developed,[14,15] they are not freely available and results are often delayed, making clinical suspicion and a thorough examination paramount factors in reaching a correct diagnosis and initiating treatment. One limitation of this study was that strain genotyping was not conducted.

Fever is seen in the majority of patients presenting with scrub typhus. It may begin insidiously with nonspecific symptoms such as headache, myalgia, diaphoresis, conjunctival congestion and vomiting following an incubation period of 7–10 days. It may be also be associated with an eschar (Figure 1) or a rash (maculo-papular or petechial) or with lymphadenopathy (local or generalized). This study shows that with meticulous examination an eschar can be detected in up to 45.5% of patients and other studies have also documented an eschar detection rate of 46–86%.[16]

Respiratory and cardiac manifestations

Respiratory symptoms are present in 20–72% of patients.[17] Cough and dyspnoea, with or without chest infiltrates, is common in scrub typhus as is evident in this study. The pulmonary involvement may vary in severity from bronchitis, mild interstitial pneumonitis to severe ARDS warranting mechanical ventilation.[18] The basic pathology in the lung is the presence of interstitial pneumonia with or without vasculitis.[19] Our study shows a significantly higher incidence of ARDS (24.9%) among our patients compared with 11–15% reported in previously published studies.[20,21] The reason for this is probably related to a referral bias, a lack of recognition of cases and a delay in referral in this population and, possibly, a higher virulence of the organism.

Wang *et al.* identified potential predictors for ARDS as hypoalbuminaemia, prolonged prothrombin time and delay in initiation of appropriate antibiotics.[20] Additional risk factors identified by Tsay *et al.* were older age, thrombocytopenia and early pneumonitis.[13] Mortality among patients who develop ARDS is high (22-45% in other studies and 60.9% in our cohort of patient).[20,21] Patients may present with ARDS without documented fever.[22]

Abnormal chest radiography is present in 59–72% of patients (42.9% in this study).[17,23] Typical findings include diffuse

Table 1 Clinical profile

	Total (N = 189)	*Dead (N = 23)*	*Survivors (N= 166)*	P *value*
Symptom				
Headache	79 (41.8)	9 (39.1)	70 (42.2)	0.782
Breathlessness	71 (37.6)	17 (73.9)	54 (32.5)	<0.001
Vomiting	70 (37.0)	11 (47.8)	59 (35.5)	0.666
Cough	57 (30.2)	7 (30.4)	50 (30.1)	0.975
Abdominal pain	41 (21.7)	4 (17.4)	37 (22.3)	0.789
Altered sensorium	42 (22.2)	11 (47.8)	31 (18.7)	0.002
Body ache/myalgia	34 (18.0)	3 (13.0)	31 (18.7)	0.772
Jaundice	25 (13.2)	2 (8.7)	23 (13.9)	0.744
Loose stools	21 (11.1)	0 (0)	21 (12.7)	0.146
Oliguria	20 (10.6)	6 (26.1)	14 (8.4)	0.021
Rash	12 (6.3)	5 (21.7)	7 (4.2)	0.008
Seizures	12 (6.3)	1 (4.3)	11 (6.6)	–
Overt bleeding manifestations	3 (1.6)	2 (8.7)	1 (0.6)	0.040
Arthritis/arthralgias	1 (0.5)	0 (0)	1 (0.6)	–
Sign				
Tachypnea (RR > 20/min)	118 (62.4)	21 (91.3)	97 (58.4)	0.002
Tachycardia (HR >100/min)	87 (46.0)	16 (69.6)	71 (42.8)	0.028
Eschar	86 (45.5)	10 (43.5)	76 (45.8)	0.835
Hepatomegaly	70 (37.0)	9 (39.1)	61 (36.7)	0.824
Respiratory crepitations	58 (30.7)	12 (52.2)	46 (27.7)	0.017
Altered sensorium	37 (19.6)	9 (39.1)	28 (16.9)	0.021
Neck stiffness	38 (20.1)	5 (21.7)	33 (19.9)	0.786
Hypotension (SBP <90 mmHg)	26 (13.8)	10 (43.5)	16 (9.6)	<0.001
Oedema	15 (7.9)	4 (17.4)	11 (6.6)	0.091
Splenomegaly	15 (7.9)	0 (0)	15 (9.0)	0.223
Lymph node enlargement	12 (6.3)	0 (0)	12 (7.2)	0.381
Rash	11 (5.8)	4 (17.4)	7 (4.2)	0.031
Conjunctival congestion	4 (2.1)	1 (4.3)	3 (1.8)	0.408
Left ventricular 3rd heart sound	2 (1.1)	1 (4.3)	1 (0.6)	0.229
Free fluid	2 (1.1)	0 (0)	2 (1.2)	–
Petechiae	1 (0.5)	0 (0)	1 (0.6)	–

	Total (mean [SD])	*Dead (mean [SD])*	*Survivors (mean [SD])*	P *value*
Investigations				
Haemoglobin (g%)	12.0 (2.3)	12.3 (2.3)	11.9 (2.3)	0.495
Total leukocyte count (cells/mm^3)	11,070.7 (5449.7)	14767.83 (6986.3)	10558.43 (5016.1)	<0.001
Differential count				
Band forms (%)	3.2 (5.5)	7.5 (10.9)	2.6 (3.9)	0.045
Neutrophils (%)	74.1 (13.6)	77.9 (13.7)	73.6 (13.6)	4.344
Platelet count (cells/mm^3)	1,10,984.6 (85898.7)	79552.2 (70955.5)	115366.1 (87063.9)	0.061
Serum creatinine (mg%)	1.3 (1.1)	1.9 (1.4)	1.2 (1.0)	0.027
Serum sodium (mmol/L)	132.4 (6.6)	134.0 (7.9)	132.2 (6.4)	0.224
Serum potassium (mmol/L)	4.1 (0.7)	4.3 (0.8)	4.1 (0.7)	0.096
Serum bicarbonate (mmol/L)	18.5 (4.6)	14.2 (4.8)	19.2 (4.2)	<0.001
Serum creatine kinase (U/L)*	919.7 (3110.9)	1891.3 (3488.7)	757.8 (3027.0)	0.106
Serum total bilirubin (mg%)	2.1 (2.4)	2.8 (2.7)	2.1 (2.4)	0.152
Serum direct bilirubin (mg%)	1.4 (2.0)	1.9 (2.2)	1.3 (1.9)	0.204
Serum total protein (g%)	6.3 (1.0)	5.9 (0.9)	6.3 (1.1)	0.051
Serum albumin (g%)	2.8 (0.6)	2.5 (0.4)	2.8 (0.7)	0.002
Serum AST(U/L)†	163.7 (138.3)	218.4 (161.2)	155.9 (133.5)	0.042
Serum ALT(U/L)‡	104.8 (70.7)	126.0 (86.9)	101.8 (67.9)	0.118
Serum ALP (U/L)§	177.9 (127.0)	216.8 (131.2)	172.5 (125.9)	0.118

	Total (%)	*Dead (%)*	*Survivor (%)*	P *value*
Chest X-ray				
ARDS pattern	47 (24.9)	14 (60.9)	33 (19.9)	<0.001
Reticulo-nodular pattern	22 (11.6)	3 (13.0)	19 (11.4)	0.727
Alveolar pattern	12 (6.3)	3 (13.0)	9 (5.4)	0.152
Hypoxia (PaO2 <80 mmHg)	65 (34.4)	17 (73.9)	48 (28.9)	<0.001
Aseptic meningitis**	39 (20.6)	5 (21.7)	34 (20.5)	0.571

*Creatine kinase was tested for 161 patients
†AST, aspartate serum transaminase (normal range 8–40 U/L)
‡ALT, alanine serum transaminase (normal range 5–35 U/L)
§ALP, alkaline phosphatase (normal range 40–125 U/L)
**The diagnosis of aseptic meningitis was assigned to patients diagnosed with scrub typhus in whom cerebrospinal fluid (CSF) analysis revealed a lymphocyte predominant pleocytosis (CSF leukocytes >5/mm^3) and negative CSF cultures. Lumbar puncture was performed on patients with neck stiiffness, altered sensorium or seizures, provided there were no contraindications for the procedure.
RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation

Table 2 Predictors of mortality (logistic regression model)

	Dead (%) (N = 23)	*Survived (%) (N= 166)*	P *value*	*Adjusted odds ratio*	*95% confidence interval*
Metabolic acidosis*	18	37	<0.001	6.1	1.773–21.272
ARDS†	14	33	<0.001	3.6	1.183–10.741
Altered sensorium‡	12	37	0.002	3.1	0.952–9.849
Shock§	10	16	<0.001	3.1	0.946–9.805
Renal failure**	11	26	0.001	1.0	0.296–3.681

*Venous bicarbonate <17 mmol/L (receiver operating characteristic curve- Se 77.3%; Sp 78.3%)
†Adult respiratory distress syndrome (bilateral pulmonary infiltrates on chest X-ray; peak flow ratio <200; normal central venous pressure)
‡Altered sensorium defined as either historical or observed altered sensorium
§Systolic blood pressure < 90 mmHg
**Serum creatinine >1.4 mg%

bilateral reticulo-nodular opacities (up to 40%), septal lines and hilar adenopathy.[19] Airspace consolidation and areas of ground-glass opacity predominantly involving the lower lobes are relatively uncommon. Pleural effusions, cardiomegaly and pulmonary oedema may also be noted.[17,19,23] Myocarditis, a reported complication, was documented in only two patients in this cohort.

Gastrointestinal and hepatobiliary manifestations

Gastrointestinal symptoms (such as vomiting, abdominal pain and loose stools) and splenomegaly have been described as being relatively common in scrub typhus.[19,24] Hepatomegaly was a common finding in this cohort of patients. The presence of gastrointestinal vasculitis has also been described.[24,25] Pancreatitis with elevated serum amylase and lipase levels in scrub typhus has been reported.[26]

The majority of patients in this cohort had elevated serum transaminases and alkaline phosphatase which is similar to previous studies.[25] However, severe hepatitis (serum transaminase levels >1000) and severe hyper-bilirubinaemia was uncommon. We observed that significant elevations of serum transaminase levels and hyper-bilirubinaemia tended to occur after patients developed septic shock and multisystem organ failure. Hepatic involvement is probably due to a predilection of the organism for the liver sinusoidal epithelial cell and resultant sinusoidal infiltration, hepatocellular cholestasis, pericholangitis and perivascular lesions in the portal area of the liver.[25]

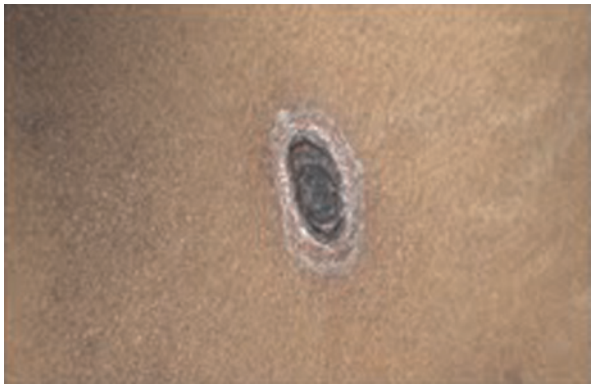

Figure 1 An eschar – a central blacked crust and erythematous halo that resembles a cigarette burn

Renal manifestations

Acute kidney injury is considered to be relatively uncommon in scrub typhus though it may sometimes be seen in severe forms.[27] It was, however, reported in 19.6% of our patients. Renal failure may occur as a result of systemic vasculitis, hypoperfusion of the kidneys secondary to shock, microangiopathy and possible direct invasion of the renal tubular cells resulting in acute tubular necrosis.[28]

Central nervous system manifestations

Neurologic involvement in scrub typhus is relatively common.[29] Aseptic meningitis and meningoencephalitis have frequently been reported and were mirrored in our cohort of patients.[30] Neurological manifestations of scrub typhus include agitation or stupor, coma, meningismus, seizures, focal deficits and papilledema.[29] The aetiopathogenesis of neurological sequelae as in other organs is a result of inflammation of the vascular lining, vascular wall and perivascular tissue resulting in micro-infarctions and ischaemia of neural tissue.[29,31] Other neurological presentations described are polyneuropathy, Guillain-Barré syndrome, brachial plexopathy, acute disseminated encephalomyelitis, intracranial haemorrhage and movement disorders.

Predictors of mortality and the sepsis syndrome

This study has identified metabolic acidosis, ARDS, altered sensorium and shock as independent predictors of mortality. Metabolic acidosis is probably a result of tissue hypoxia secondary to vasculitis, acute kidney injury and shock with resultant lactic acidosis.

In our study 26 (13.8%) patients presented with shock, refractory to fluid challenge and requiring inotropic support associated with multisystem organ failure: 10 of these patients died. Scrub typhus in severe forms results in an inflammatory cascade resulting in severe sepsis with multiorgan dysfunction requiring intensive care, inotropic support and mechanical ventilation. As a result, these patients have a high mortality. The determinants of severity have not been clearly identified, although virulent strains, host factors, nutritional status, concomitant infections, delayed presentation and age may each have roles to play.[12,13] Hypoalbuminaemia is more severe in patients with poor outcomes ($P = 0.002$). Hypoalbuminaemia probably occurs as a result of the presence of a severe infection and, secondly, due

to seepage of albumin into the perivascular spaces following severe vascular injury.[25]

It appears that scrub typhus in this cohort of patients from South India predominantly have four basic, but overlapping, presentations: (1) mild disease (mild elevation of hepatic transaminases, leucocytosis and thrombocytopenia) with or without a rash; (2) respiratory disease; (3) central nervous system disease with meningoencephalitis; and (4) sepsis syndrome with multisystem organ dysfunction.

Conclusion

There should be a high index of suspicion of scrub typhus for patients presenting with AFI in endemic areas who have any of the above presentations. An eschar should be meticulously sought. Treatment with doxycycline with a rapid therapeutic response provides further confirmatory evidence for the diagnosis of scrub typhus. Mortality is high, especially if the diagnosis and treatment are delayed. Given the telltale presence of an eschar, characteristic clinical profile and the dramatic therapeutic response to a cheap, yet effective drug such as doxycycline, medical practitioners in the region have ample opportunity to reach an early diagnosis and initiate treatment, thus reducing the mortality and morbidity associated with scrub typhus.

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