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Scrub Typhus: Epidemiology, Clinical Presentation, Diagnostic Approach, and Outcomes

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Abstract

Scrub typhus is an acute febrile illness. The causative organism, Orientia tsutsugamushi, is transmitted by the larvae (or chiggers) of several species of Trombiculid mites. Scrub typhus is endemic and re-emerging in Eastern and Southern Asia, Northern Australia, and islands of the Western Pacific and Indian Ocean. Scrub typhus is grossly under-diagnosed in India due to its non specific clinical presentation, limited awareness, and low index of suspicion among clinicians, and the lack of diagnostic facilities.

Objectives: To study the clinical presentation, diagnostic approach, complications, management and outcome in scrub typhus patients in a tertiary care hospital in Kota district of Rajasthan during the period from August 2017 to November 2018.

Methods: This is a prospective epidemiological study of 160 patients with febrile illness diagnosed as scrub typhus with positive serology at a tertiary care hospital in Kota.

Results: 160 patients above the age of 14 years who presented with the chief complaint of fever. Some of them also had vomiting, pain abdomen, dyspnoea. In laboratory findings, most of them had low platelet level, elevated liver enzymes, raised serum LDH, raised triglycerides level and hypo albuminaemia. Various complications like ARDS, acute renal failure, ascites, pleural effusion, multiple organ dysfunction, and encephalopathy were observed in many patients. Diagnosis of scrub typhus was confirmed by Immunochromatography test for IgM antibodies and IgM ELISA test. 60% patients recovered and were discharged after 4 - 5 days treatment but 36 - 37% patients had to stay 10 or more days due to complications and 6 patient out of 160 did not survive.

Conclusion: Scrub typhus has emerged as an important cause of febrile illness in this region of India. Empirical treatment with Azithromycin and/or Doxycycline is justified in endemic areas.

Keywords: Eschar, immunochromatography, Orientia tsutsugamushi.

Introduction

Scrub typhus is a mite borne disease caused by *Orientia tsutsugamushi*'. It is distributed throughout Asia Pacific, being endemic in Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia and northern parts of Australia[1]. Scrub typhus often presents as fever, headache, muscle pain and abdominal pain which is clinically indistinguishable from other endemic diseases such as typhoid, leptospirosis, and dengue. Eschar is a useful indicator of scrub typhus infection but has variable rate of occurrence[2-5]. It may point towards diagnosis but is present in only a few patients and requires vigilant examination. The organism infects vascular endothelium with subsequent vascular injury in organs like the skin, liver, kidneys, meninges and brain resulting in multi-organ manifestations. Diagnosis depends on a high index of clinical suspicion and laboratory confirmation. There has been a sudden spurt of cases reporting to our hospital, with about 160 cases diagnosed within a period of 16 months from August 2017 to November 2018 who tested positive by Immunochromatography and IgM ELISA test. They responded well to oral Doxycycline and/or Azithromycin.

Material and methods

This was a prospective study of patients with Scrub typhus admitted to our hospital. The study group included patients aged more than 14 years admitted to the medical wards of a tertiary care hospital, in Rajasthan, over a period of 16 months (August 2017 to November 2018). All patients admitted with a history of fever and/or headache, and myalgia of more than three days duration were evaluated for Scrub typhus after ruling-out dengue, malaria, and enteric fever by serology, peripheral smear, and blood culture, as appropriate. The other investigations carried-out included complete blood counts, liver function test, renal profile, serum electrolytes, chest X-ray, urine culture, blood gas analysis, hepatitis markers, ultrasound of the

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abdomen, CSF and MRI brain were done if indicated. A rapid immunochromatography assay for detection of IgM/IgG or IgA antibody in human serum against *Orientia tsutsugamushi* antigen and IgM ELISA in clinically suspected cases after ruling-out other possible causes by relevant investigations was used. An informed written consent was obtained from all patients for the study.

Exclusion criteria

1. Patients with previous liver or kidney failure, recent cerebral events (stroke, meningoencephalitis) and hepatitis were excluded.
2. Patients with concurrent infection with malaria, chikungunya, or dengue fever.

An approval for the study was taken from the institutional ethics committee.

Results

160 patients in the age range of 14 - 75 years (85 males and 75 females) directly or indirectly engaged with agriculture, majority from rural area tested positive for IgM/IgG antibodies to *Orientia tsutsugamushi*.

Mean age of cases was 39.86 ± 13.42 years. Mean age in males was 40.83 ± 13.79 years and in females was 38.77 ± 12.90 years. There was no statistically significant difference in the mean ages of males and females (P = 0.33) (Table III).

Maximum patients reported in the month of September 2017 and September 2018. 78% patients were admitted in monsoon and post-monsoon period. It indicats that maximum chances of scrub typhus outbreak are in rainy season (Table I).

Out of 85 males, 68 were from rural area and out of 75 females, 62 belonged to rural area (Table II).

Majority of patients were involved in farming and cattle breeding (Agriculture), directly or indirectly (Table IV).

Fever was the most common presenting symptom in all patients. Majority had fever for less than 1 week. Maximum duration of fever was 1 month. Mean duration of fever was 6.4 days. Other common symptoms were myalgia (30%), nausea, vomiting (31.25%), abdominal pain (20%). The signs noticed were eschar (3.75%), hepatomegaly (30%), and splenomegaly (31.25%).

Presenting symptoms and findings on clinical examination are shown in Table V and VI, respectively. Eschar was found in 6 patients, most commonly in groin, back and lower extremities. The blood counts showed leucopenia in (11.87%) cases and leucocytosis in (28.75%) cases. Thrombocytopenia was noted in (67.5%) patients and mean platelet counts were 1.21 Lakh/mm^3. Elevation of AST and ALT was noted in (68.75%) patients. Laboratory findings are shown in Table VII.

Table I: Seasonal or monthly distribution of cases.

Month	2017	2018
January	–	5
February	–	4
March	–	2
April	–	2
May	–	1
June	–	1
July	–	2
August	8	7
September	30	26
October	20	18
November	15	12
December	6	–

Table II: Rural or urban distribution of cases.

Category	Male (n = 85)	Female (n = 75)
Rural	68	62
Urban	17	13

Table III: Distribution of patients according to age and gender.

Age in years	Male (n = 85)	Female (n = 75)	Total (n = 160)
< 20	4	3	7
20 - 40	32	28	60
40 - 60	36	32	68
> 60	13	12	25

Table IV: Distribution of patients based on occupation.

Occupation	Male (n = 85)	Female (n = 75)
Agriculture	63	58
Other	22	17

Various complications were observed in this study and are shown in Table VIII. Renal failure was noted in 30 patients (18.75%) out of which 5 required dialysis. Out of these 5 patients, 4 improved after one session of haemodialysis and only one patient required 2 sessions of dialysis, but all 5 survived after haemodialysis and other supportive treatment.

Table V: Presenting symptoms in scrub typhus.

Presenting symptoms	No. of patients (n = 160)
Fever	All (100%)
Headache	31 (19.37%)
Myalgia	48 (30%)
Vomiting	50 (31.25%)
Abdominal pain	32 (20%)
Cough	15 (9.37%)
Dyspnoea	25 (15.62%)
Shock	14 (8.75%)
Altered sensorium	13 (8.125%)

Table VI: Clinical examination findings in scrub typhus.

Clinical finding	No of patients
Hepatomegaly	48 (30%)
Splenomegaly	50 (31.25%)
Anaemia	58 (36.25%)
Hepatosplenomegaly	30 (18.75%)
Eschar	6 (3.75%)
Meningeal sign	6 (3.75%)
Lymphadenopathy	3 (1.875%)

Table VII: Laboratory findings in scrub typhus.

Laboratory findings	No. of patients
Anaemia (Hb < 11 gm/dl)	58 (36.25%)
Leucopenia (< 4,000 cells/mm^3)	19 (11.87%)
Leucocytosis (> 10,000 cells/mm^3)	46 (28.75%)
Thrombocytopenia (< 1,50,000/mm^3)	108 (67.50%)
Severe thrombocytenia (< 20,000/mm^3)	8 (5%)
Elevated liver enzymes	110 (68.75%)
Serum LDH (> 480 IU/L)	70 (43.75%)
Serum Triglyceride (Fasting > 200 mg/dl)	80 (50%)
Hypoalbuminaemia (3.5 gm/dl)	112 (70%)
Hyponatraemia (< 135 meq/1)	36 (22.5%)
Hypokalaemia (< 3.5 meq/1)	23 (14.37%)
Chest infiltrates (interstitial pneumonia b/l reticulonodular opacity in chest X-ray)	38 (23.75%)
Pleural effusion	37 (23.125%)
CSF WBC (> 5 cells/mm^3)	6 (3.75%)

Table VIII: Complications of scrub typhus.

Complications	Number of patients
ARDS	22 (13.75%)
Acute renal failure	30 (18.75%)
Electrolyte disturbance	48 (30%)
Polyserositis	15 (9.37%)
MODS	22 (13.75%)
Encephalopathy	6 (3.75%)
Death	6 (3.75%)

Table IX: Clinical and laboratory difference between non severe and severe cases of scrub typhus according to category.

Parameters	Cat 1 (non severe) n = 96 (60%)	Cat 2 (severe) n = 48 (30%)	Cat 3 (very severe or fatal) n = 16 (10%)
Renal profile (AKI)	May or may not be deranged Mean serum creatinine (1.01 ± .33 mg/dl)	Deranged Mean creatinine (2.67±1.29 mg/dl) Dialysis not required	Deranged Mean creatinine (6.8 ± 1.83 mg/dl) Significantly high Dialysis required
Liver function test SGOT/SGPT	Raised in 56 out of 96 (58.33%)	Deranged in 40 out of 48 (83.33%)	Deranged in 14 out of 16 (87.5%)
Respiratory failure (ARDS)	Nil	May or may not be present. Present in (15, 31.35%). Invasive mechanical ventilation not required	Present in (7, 43.75%). Invasive mechanical ventilation required
MODS	Nil	12	10
Encephalopathy	Nil	Nil	Yes (6 out of 160)
Death	Nil	Nil	Yes (6 out of 160)

ARDS was reported in 22 (13.75%) patients, out of which 10 improved after 3 - 4 days treatment with high flow oxygen via nasal canula, i/v fluid and other supportive measures. 5 patients required non invasive positive pressure ventilation support and survived after average 3 days of ventilation support. 7 patients required invasive mechanical ventilation. The mean duration of ventilator support was 3.5 days. Out of 7 patients, 2 died after 5 days of mechanical ventilation support and ICU care.

15 (9.37%) patients had polyserositis, of which 14 had both ascites and pleural effusion and only one patient had pleural effusion and pericardial effusion.

13 patients presented with altered sensorium, of which 7

improved after intravenous sodium.

Table X: Outcome of disease in patients.

Outcome	No. of patients/days
Mechanical ventilation required	12
• Non invasive	5
• Invasive	7
• Both	5
• Average duration of non-invasive ventilation	3 days
• Average duration of invasive ventilation	3.5 days
Need for dialysis	5
Average duration of ICU stay	4.5 days
Average duration of hospital stay	5.4 days
Mortality	6 patients

36 (22.5%) patients had hyponatraemia who required intravenous sodium. Among other electrolytes hypokalaemia (serum potassium < 3.5 mEq/l) was also noted in 23 (14.37%) patients but intravenous potassium was not required in any patient.

Brain MRI and CSF (cerebrospinal fluid) examination was done in 6 patients, who had encephalopathy.

MRI findings:

1. 3 patients showed diffuse subcortical and periventricular white matter lesions.
2. 2 patients showed microhaemorrhages and white matter changes in deep white matter areas.
3. 1 patient showed diffuse cerebral oedema.

CSF findings among encephalopathy patients: All encephalopathy patients CSF showed lymphocytic pleocytosis and normal protein and sugar level. CSF PCR to identify the organism in CSF was not done in this setting because of poor availability of resources.

Duration of hospital stay was less than 5 days in non-severe patients (60% of all cases). 30% of patients (severe cases) had to stay for 6 - 10 days due to some complications. 10% (very severe cases) patients needed more than 10 days of hospitalisation because of severe complications like ARDS, acute renal failure, MODS, encephalopathy. According to the severity of disease, clinical and laboratory parameters, patients were divided into 3 categories; non-severe, severe, and very severe patients.

Category 1 (non severe):

Patients with mild symptoms like fever, myalgia, cough, vomiting and mild derangement of laboratory parameters without any complications were included in this category. Majority patients in this category had history of fever < 7 days. Mean duration of symptoms was 3.8 days. Duration of hospital stay in these patients was ≥ 5 days. Mean duration of hospital stay was 3.5 days. All these patients were treated with monotherapy with Doxycycline and other symptomatic measures. There was no comorbidity in these patients.

Cetagory 2 (severe):

Patients with symptoms more severe then category 1, such as dyspnoea, altered sensorium, shock, thrombocytopenia (< 1,00,000/mm^3), electrolyte imbalance, acute kidney injury (but not requiring dialysis), pleural effusion, b/l chest infiltrates, MODS, ARDS (but not requiring mechanical ventilation support) were included in the second category. Duration of symptoms was 7 to 14 days with a mean of 8.5 days. Duration of hospital stay in this category was 6 to 10 days. Mean hospital stay in this category of patients was 6.5 days. No significant relationship between these patients and other comorbidities like hypertension, diabetes and CAD was found. All these patients were treated with dual therapy with capsule Doxycycline 100 mg twice a day for 7 - 10 days and injection Azithromycin 1 gm per day for 5 - 7 days and other symptomatic measures like correction of sodium, oxygen therapy, i/v fluids, and dopamine therapy.

Category 3 (very severe/fatal):

Patients with more severe symptoms like severe dyspnoea, altered sensorium with meningeal signs, very low platelets count (< 20,000/mm^3), acute kidney injury patients (who required haemodialysis), patients with MODS with poor response to treatment, ARDS patients (who required mechanical ventilation support and ICU care) were included in this category 3. Duration of symptoms in this category was more than 2 weeks and mean was 12.5 days. Patients in this category had to stay in hospital more than 10 days with maximum stay of 21 days and mean duration of 13.5 days.

Patients in this category were treated with dual therapy with Azithromycin and Doxycycline and symptomatic measures. There was no specific and significant correlation found in patients with category 3 and other comorbidities like hypertension and diabetes and CAD. 6 patients in this category could not survive despite intensive management and care. One major aspect was that all these patients reported late to hospital and delay in diagnosis and starting treatment was the main cause of severity of illness.

So, according to this study, severe respiratory distress, low urine output, altered sensorium, low oxygen saturation, high

serum creatinine level, deranged arterial blood gas analysis are early predictors of mortality and also delay in diagnosis and treatment can result in severe complications and increased mortality.

Fig. 1: *Eschar on back.*

Fig. 2: *Eschar on front of arm.*

Discussion

Tropical diseases are defined as diseases that are prevalent in, or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation[6]. Most often disease is transmitted by an insect "bite", which causes transmission of the infectious agent. The Indian subcontinent by its very location represents one of the largest tropical and subtropical regions with many of these infections being prevalent. Some of these occur throughout the year and some are greatly influenced by the seasons (especially rainy season) and geography[7]. On the basis of limited epidemiologic data from the North (Rohtak) and South (Vellore) and overall experience of the group, it was decided to focus on seven most common infections, with reference to other infections wherever appropriate[8-10]. These are dengue, rickettsial infections especially Scrub typhus, malaria (usually due to *Plasmodium falciparum*), typhoid, and leptospirosis; bacterial sepsis and common viral infections like influenza. Rickettsial infections have been documented from various parts of India[11]. There have been reports of sporadic outbreaks of scrub typhus mainly in the eastern and southern Indian states with serological evidence of widespread prevalence of spotted fevers and scrub typhus[12,13], particularly during the monsoon and post-monsoon months[14,11,15,16]. The outbreak that we studied also occurred during the same period.

Age, sex, residential area, and occupation are known to influence the occurrence of scrub typhus. Most of our patients were 20 - 60 years of age, an observation similar to that of Sinha *et al*[17] and Madi *et al*[18]. More men were affected in our series, same as in the study by Rajoor *et al* who reported more men to be affected[19].

We considered the duration of symptoms from the time of onset of fever as this was the first symptom in most patients. Two-third of patients were diagnosed in the first week.

Eschar at the site of attachment of the larval mite/chigger is considered highly suggestive of scrub typhus, but occurs in a variable proportion of patients in different studies[20]. It is a blackish necrotic lesion resembling a cigarette burn generally found in areas where the skin is thin, moist or wrinkled, and where the clothing is tight such as over the abdomen, groin, and on the legs[19]. Its presence is considered pathognomonic of the disease, but its absence does not exclude the possibility of scrub typhus. However, it is relatively difficult to detect on dark-skinned patients[21]. In our study, eschar was present in 6 (3.75%) patients and the most common site was the groin and back. While similar rates (4% - 12%) have been reported by some Indian studies[19,22,15], Vivekanandan *et al*[14] (46%), Chrispal *et al*[9]

(45.5%) and studies from Vietnam[23], Taiwan[24], and Korea[25] reported slightly higher incidences of eschar probably due to fair-skinned population of these studies, which increases the chances of finding eschar. Our findings were similar to those by Razak *et al* who concluded that the occurrence of eschar is less frequent among patients from South-east Asia[26].

Eschar is more often than not associated with regional lymphadenopathy. Only 3 (1.87%) of our patients had lymphadenopathy. A wide range (22% - 53%) of lymphadenopathy has been reported in different studies[14,19,22,17], and some have suggested that the presence of generalised lymphadenopathy suggests a late presentation and a worse outcome[22].

The abnormalities in cell counts, and liver and renal functions in our patients were consistent with those reported in other studies[14,19,15,18].

Among our patients who presented with any central nervous system manifestations, 13 required CSF examination and only 6 had confirmed meningitis. However, Viswanathan *et al* had 17 patients with meningitis among 65 of their patients[27]. This is possibly because they specifically searched for patients with scrub typhus and meningitis. Scrub typhus should be considered in the differential diagnosis of 'subacute' meningitis, especially when accompanied by renal failure or jaundice[28]. Previous studies from India have reported meningoencephalitis in 9.5% - 23.3% of patients[14,13,16].

Scrub typhus is a cause of multi-organ dysfunction (MOD). 22 patients (13.75%) had two or more organ systems involved. Complications in scrub typhus develop after the first week of illness. Narvencar *et al* found hepatic dysfunction to be the most common followed by ARDS, circulatory collapse, and acute renal failure[29]. We found respiratory dysfunction in over two-thirds of patients, followed by renal dysfunction in over half the patients.

In our study, respiratory failure was present in 22 patients, so 22 of our patients (13.75%) required mechanical ventilation. Of these, 15 were managed with only non-invasive ventilation, 7 required non-invasive ventilation to be changed to invasive mechanical ventilation. A study from southern India showed involvement of the respiratory system in 76.9% of patients and requirement of ventilatory support in 68.9% of patients[13].

The mortality in patients with scrub typhus has wide variations and depends on the circulatory load of *O. tsutsugamushi*, early or late presentation and treatment modality. Deaths are attributable to delayed presentation or diagnosis, and drug resistance. Complications such as ARDS, renal failure, and hepatic involvement are independent predictors of mortality; most of these were present in our patients[30].

The case fatality rate for scrub typhus has been 7% - 30%[31], including 10% in Korea[32] to 30% in Taiwan[33]. The mortality rate of 3.175% in our study was lower compared to other studies from India by Mahajan *et al* (mortality 14.2%)[16], Kumar *et al* (mortality 17.2%)[34], Rungta *et al*[35], Lai *et al* (mortality 15% - 30%)[33] and Griffith *et al*[36]. Studies have shown inter-strain variability in virulence[32] and since we did not do serotyping and genotyping, it is possible that the strain type present in our region was a less virulent one causing lower case fatality. Another reason is early diagnosis and treatment for scrub typhus without waiting for the reports.

100 patients selected at random who tested positive by immununochromatography were also tested by IgM ELISA for Scrub typhus infection and found to be positive. All the patients who tested positive had a good clinical correlation, supportive laboratory findings, and a dramatic response to treatment with doxycycline and azithromycin. The rapid immunochromatography assay used in our study uses major surface protein 56 KDa antigen of *O. tsutsugamushi* (Karp, Kato, and Guilliam). This test has a sensitivity of 99% and specificity of 96%. This test has been compared with a traditional IFA in a study from China[37] and found to be more sensitive and suitable for use in developing countries.

Diagnosis of scrub typhus is difficult in India because of its varied clinical presentation, absence of eschar in many patients, and lack of availability of specific tests (ELISA/ serological tests). In developing countries with limited resources such as India, we suggest that the diagnosis of scrub typhus should be based largely on a high index of suspicion and careful clinical, laboratory, and epidemiological evaluation. It is prudent to recommend empirical antibiotic therapy in patients with acute febrile illness with evidence of multi-organ involvement.

Conclusion

It is concluded that a high index of clinical suspicion is required for diagnosis of scrub typhus due to varied clinical presentations. Rapid Immunochromatography tests based on detection of specific antibodies and IgM ELISA test is a useful laboratory aid in the diagnosis. Doxycycline and/or Azithromycin result in a dramatic improvement in a majority of patients. The impact of comorbidities like diabetes and CAD on severity of illness could not be well established.

Abbreviations

MODS - Multiple organ dysfunction syndrome

AKI - Acute kidney injury

ARDS - Acute respiratory distress syndrome

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