

Emergence of Scrub Typhus in Northern India: Experience from Tertiary Care Hospital

Kuzey Hindistan'da Çalılık Tifüsünün Yeniden Ortaya Çıkışı: Bir Üçüncü Basamak Hastanesi Deneyimi

Hari Krishan Aggarwal, Deepak Jain, Vipin Kaverappa, Anshul Mittal, Sachin Yadav, Abhishek Gupta
Pt. B. D. Sharma Postgraduate Institute of Medical Sciences, Department of Medicine, Rohtak, India

Abstract

Objective: We undertook this study in view of sudden outbreak of acute febrile illness, with associated thrombocytopenia and multiorgan failure, to assess the underlying etiological agent in these cases occurring in the district of Haryana, Northern India.

Methods: Adult patients with acute febrile illness who visited out-patient and emergency department, from July to November 2012 were examined. Suspected cases were tested for specific IgM antibodies against *Orientia tsutsugamushi*.

Results: Among 25 seropositive cases, 22 (88%) presented from July to September, while 3 (12%) during October and November. Mostly patients presented with fever (88%), hypotension (40%), maculopapular rash (28%) mostly on face and trunk, eschar (12%) predominantly over lower limbs and pleural effusion (12%). Abnormal liver function tests were seen in the form of elevated transaminases (84%) and serum alkaline phosphatase (72%). Anemia (36%), leukocytosis (32%) and thrombocytopenia (72%) were also detected. Proteinuria was found in 64% of patients while 40% had increased blood urea on presentation. The most common complications were shock in 32% and acute respiratory distress syndrome (ARDS) in 20% of the patients, eventually requiring ventilator support. Patients were treated with doxycycline 100 mg bid for 12-14 days. Three patients could not recover despite the addition of azithromycin and injectable chloramphenicol apart from doxycycline, and succumbed to the illness giving a mortality rate of 12%.

Conclusions: Scrub typhus forms one of the most differentials in patients of acute febrile illness presenting with thrombocytopenia, shock, abnormal liver function tests, renal dysfunction, ARDS and multiorgan dysfunction. Measures avoiding direct contact with infected mites and reducing the time of contact of mites with the body coupled with early diagnosis and treatment should be considered to prevent the development of fatal complications.

Klimik Dergisi 2014; 27(1): 6-11.

Key Words: Scrub typhus, eschar, thrombocytopenia, acute respiratory distress syndrome.

Özet

Amaç: Bu çalışmanın amacı, Hindistan'ın kuzeyinde Haryana Eyaletinde aniden başlayan, trombositopeni ve çoğul organ yetmezliğinin eşlik ettiği akut bir ateşli hastalık salgınının etyolojik etkeninin belirlenmesidir.

Yöntemler: Temmuz-Kasım 2012 arasında akut ateşli bir hastalık nedeniyle poliklinik ve acil servise başvuran erişkin hastalar incelendi. Kuşku olgular *Orientia tsutsugamushi*'ye karşı özgül IgM antikorları yönünden test edildi.

Bulgular: Bu çalışmada seropozitif olarak bulunan 25 olgudan 22 (%88)'si Temmuz ve Eylül ayları arasında, üçü (%12) ise Ekim ve Kasım aylarında ortaya çıkmıştı. Hastalardaki en sık belirti ve bulgular, ateş (%88), hipotansiyon (%40), daha çok yüz ve gövdede olan makülopapüler döküntü (%28), daha çok alt ekstremiteler üzerinde olan eskar (%12) ve plevral epanşmandı (%12). Karaciğer fonksiyon testlerindeki bozukluklar, transaminaz (%84) ve serum alkalin fosfataz yükselmeleri (%72) biçimindeydi. Ayrıca anemi (%36), lökositoz (%32) ve trombositopeni (%72) de saptandı. Başvurduklarında hastaların %64'ünde proteinüri bulunurken kan üresi yükselmesi %40'ında vardı. En sık komplikasyonlar olarak hastaların %32'sinde şok ve %20'sinde ventilatör desteği gerektiren akut solunum sıkıntısı sendromu (ARDS) gözlemlendi. Hastalar 12-14 gün süreyle 2x100 mg doksisisiklinle tedavi edildi. Doksisisiklinin yanı sıra azitromisin ve parenteral kloramfenikol eklenmesine karşın ölen üç hastayla mortalite hızı %12 oldu.

Sonuçlar: Trombositopeni, şok, karaciğer fonksiyon testlerinde bozukluklar, böbrek fonksiyon bozukluğu, ARDS ve çoğul organ yetmezliğiyle kendini gösteren akut ateşli hastalıkların çok sayıdaki ayırıcı tanı olasılıklarından birini de çalılık tifüsü oluşturmaktadır. Ölümcül komplikasyonların gelişmesinden korunmak için infekte akarlarla doğrudan temastan kaçınılmasına ve akarların vücuda temas etme süresinin kısaltılmasına yönelik önlemlerle birlikte erken tanı ve tedavi düşünülmelidir.

Klimik Dergisi 2014; 27(1): 6-11.

Anahtar Sözcükler: Çalılık tifüsü, eskar, trombositopeni, akut solunum sıkıntısı sendromu.

Address for Correspondence / Yazışma Adresi:

Deepak Jain, Pt. B. D. Sharma Postgraduate Institute of Medical Sciences, Department of Medicine, Rohtak, India
Phone/Tel.: +91 941 614 78 87 Fax/Faks: +91 126 221 13 08 E-mail/E-posta: jaindeepakdr@gmail.com
(Received / Geliş: 18 May / Mayıs 2013; Accepted / Kabul: 12 March / Mart 2014)

DOI: 10.5152/kd.2014.03



Introduction

Scrub typhus is an acute febrile illness caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*. An estimated one billion people are at risk for scrub typhus and an estimated one million cases occur worldwide, annually. Mortality rates range from 7-30% depending on the geographic area and the time of intervention (1-4). In India, the presence of scrub typhus has been documented for several decades (5). After an occurrence among troops during World War II in Assam and West Bengal and in the 1965 Indo-Pakistani war, it had gradually faded into oblivion in post-war era. However, a surge in the cases reported from all parts of the country in recent times has renewed our interest in this "once-forgotten" disease. There have been cluster of cases reported from states of Maharashtra, Assam, Tamil Nadu, Uttaranchal, Himachal Pradesh, West Bengal, Kerala, Karnataka, and Jammu and Kashmir (6-9).

We undertook this study in view of sudden outbreak of acute febrile illness, with associated thrombocytopenia and multiorgan failure, to assess the underlying etiological agent in these cases.

Methods

Our hospital is a tertiary centre catering to the patients of state of Haryana. Adult patients (age more than 14 years) with acute febrile illness who visited our out-patient and emergency department, between July 2012 and November 2012 were examined.

Our study is limited to the district of Haryana, represented by dry plains and semi-desert area with minimal annual rainfall; geographically unlikeliest area to harbinger an epidemic of scrub typhus. Although, the diagnosis of scrub typhus occupied the lowest rung among all the differentials of acute febrile illness, it was considered since patients clinical presentation was classical with rickettsiosis, and all the tests run to identify the most commonly prevalent etiological agents were negative.

A detailed history with special consideration to their occupation and area of residence was obtained. Each patient was subjected to detailed clinical examination with meticulous search for features like rash, eschar, icterus, hepatomegaly and splenomegaly. Basic laboratory tests like complete blood counts, peripheral blood film, absolute platelet count, serum electrolyte, urine complete analysis, liver function tests (LFTs), kidney function tests (RFTs), blood gas analysis and prothrombin time were carried out. In addition, tests like chest X-ray, abdominal ultrasound and computerized tomography (CT) scan, if required, were done. These patients were also subjected to other tests including blood culture, Widal test, rapid antigen card test for malaria, serology for dengue and leptospirosis. Investigations like urine culture, sputum culture and stool examination were done if history and examination suggested infections related to these sites.

In patients of acute febrile illness with ≥ 2 of following features, thrombocytopenia, shock, deranged LFTs, deranged RFT and in patients not responding to standard antimalarial (artesunate+clindamycin) and conventional antibiotic therapy, samples were tested for specific IgM antibodies against *O. tsutsugamushi* using ELISA at the National Centre for

Disease Control (NCDC), New Delhi (India) which is a WHO approved central government India authority for conducting these tests. Blood samples of around 100 patients 29 of which had positive serology were sent for analysis. The patients with any complications of disease were admitted for in-patient treatment and further investigation.

Case definitions were made as follows: Any patient with acute febrile illness [1] who had clinical and laboratory features suggestive of scrub typhus; [2] who were found to be negative for common diseases prevalent in this area including malaria, dengue, leptospirosis and typhoid, and [3] who were positive for scrub typhus by IgM ELISA.

Results

Of 29 patients who had a positive serology for scrub typhus, four were excluded, since two patients had malarial coinfection and two were diagnosed of dengue concomitantly.

25 patients who fulfilled the aforementioned criteria were included as "case" in this study. Their age ranged between 18 to 70 years. The male to female ratio was almost equal with 13 males and 12 females respectively. Most of the patients hailed from the district of Rohtak and its surrounding districts, including Jajhhar, Rewari, Bahadurgarh, Sonapat and Jind. Among 25 cases, 22 (88%) presented from the month of July to September, while 3 (12%) presented during the cooler months of October and November.

The signs and symptoms of patients were studied and are summarized in Table 1. Among 25 patients, 88% had fever which ranged from a duration of 5-10 days, low to high grade and was associated with chills and rigor in large majority of them. 40% of the patients presented with hypotension, three of whom required inotropic support. A maculopapular rash was present in 28% patients mostly on face and trunk. Eschar was found in only 12% of the patients predominantly over lower limbs (Figure 1). Pleural effusion was detected in 12% of the patients, which revealed a transudative picture on diagnostic aspiration done under aseptic conditions. Hepatosplenomegaly if suspected clinically was confirmed by ultrasonography and was detected in 18 of our patients which comprised greater than 2/3 of study group.

Table 1. Clinical Features of Patients with Scrub Typhus (n=25)

Signs and Symptoms	Number	(%)	Signs and Symptoms	Number	(%)
Fever (>100°F)	23	(92)	Crackles	8	(32)
Myalgia	16	(64)	Rash (maculopapular)	7	(28)
Headache	15	(60)	Diarrhea	6	(24)
Nausea and vomiting	13	(52)	Lymphadenopathy	5	(20)
Breathlessness	12	(48)	Altered sensorium	4	(16)
Abdominal pain	12	(48)	Pleural effusion	3	(12)
Systolic blood pressure <90 mmHg	10	(40)	Eschar	3	(12)
Hepatomegaly	10	(40)	Icterus	3	(12)
Splenomegaly	9	(36)	Oliguria	3	(12)



Figure 1. A typical eschar located anterolaterally over the distal part of the right leg.

Among the biochemical parameters, abnormal LFTs in the form of elevated transaminases (84%) and serum alkaline phosphatase (72%) were most commonly observed. Anemia in 9 (36%), leukocytosis in 8 (32%) and thrombocytopenia in 18 (72%) were also detected. Although leukopenia is not commonly associated with rickettsial infection; was found in 44% of patients. Proteinuria when assessed by dip stick was found in 16 (64%) of patients. 10 (40%) had increased blood urea on presentation while 6 (24%) had elevated serum creatinine level. Hyponatremia was seen in 10 (40%) of patients. 8 (20%) of patients had abnormal chest X-ray which revealed bilateral diffuse parenchymal infiltrate, ground glass opacities, bilateral reticulonodular opacities, septal lines, consolidation, hilar lymphadenopathy and pleural effusion (Table 2).

The most common complication observed was shock, 8 (32%) of the patients presenting with the same. Although 20% among them responded to fluid resuscitation alone, 12% had to be supported with inotropes to sustain their blood pressure above minimum recommended levels. Acute respiratory distress syndrome (ARDS) complicated the clinical course of scrub typhus in 5 (20%) of the patients, eventually requiring ventilator support. Clinical features of meningitis were elicited in 2 (8%) of the patients; their lumbar puncture revealed abnormal cerebrospinal fluid (CSF) picture with increased proteins and lymphocytic pleocytosis. 4 (16%) of patients suffered from renal failure with half of them requiring

haemodialysis. Disseminated intravascular coagulation (DIC) was present in two of our patients with prolonged prothrombin time, activated thromboplastin time and increased fibrin degradation products (FDP) levels. Similarly, myocarditis was suspected in 3 (12%) of our patients on basis of nonspecific ST-T wave changes on electrocardiography (ECG) and was confirmed by 2D-echocardiograph.

Patients were treated with doxycycline 200 mg bid for 12-14 days, while azithromycin, 500 mg qd, was administered to patients who failed to respond to doxycycline therapy. Patients who were afebrile following treatment were discharged in stable condition and advised follow up every week for a period of 1 month with regular monitoring of their platelet count, LFTs, RFTs and chest X-ray. Among 14 (56%) of the patients who maintained regular follow, these parameters returned to normal and they remained afebrile, while 8 (32%) were lost to follow-up although they were afebrile on their last visit. One of our patients was pregnant and was treated with azithromycin from the outset. Three of our patients could not recover despite the addition of azithromycin and injectable chloramphenicol apart from doxycycline, and succumbed to the illness giving a mortality rate of 12%.

Discussion

Scrub typhus is a re-emerging infectious disease in India. The causative organism is a Gram-negative obligate intracellular pathogen; *O. tsutsugamushi*, which belong to *Orientia* genus of family *Rickettsiaceae*. The true reservoir of infection is the trombiculid mite (*Leptotrombidium delinense* and *L. akamushi*), while larval mite (also known as chigger) act as the primary reservoirs. The disease is transmitted to larva by trans-ovarian and trans-stadial route. The human are infected accidentally by the bite of an infected chigger when they encroach on to a mite infested area (10). The incubation period of disease varies from 6 to 21 days (11). It is generally incapacitating and notoriously difficult to diagnose as signs and symptoms are nonspecific and overlap with common prevalent disease like malaria, dengue, leptospirosis and typhoid. Untreated cases can have high fatality rates, but when diagnosed early they are often easily treated.

Despite acknowledging its presence for the last few decades, it had remained a grossly underdiagnosed disease in India predominantly due to its nonspecific clinical features, limited awareness, lack of suspicion, and unavailability of diagnostic tests. Attributing its clinical features erroneously to malaria, of course, is rampant in this part of the world, despite lack of concrete evidence, coupled with the dramatic response to anti-malarial treatment which invariably incorporates doxycycline as a component, has led to underestimation of this disease despite its significant presence. Our national programmes largely dedicated towards control of malaria, and to some extent dengue fever had almost relegated scrub typhus to pages of public health textbooks up until recent reports have emerged from various parts of India, especially from sub-Himalayan belts and Western Ghats, compelling the clinicians and epidemiologist alike, to provide this treatable yet fatal disease its due credit.

It occurs mostly in rainy and hilly areas with moisture and scrub vegetation, however it can also occur in diverse habi-

Table 2. Laboratory Parameters of Patients with Scrub Typhus (n=25)

Laboratory Finding	Number	(%)	Laboratory Finding	Number	(%)
Anemia (Hb <10 g/dL)	9	(36)	Proteinuria	16	(64)
Total leukocyte count			Thrombocytopenia	18	(72)
<4000/mm ³	11	(44)	<50 000/mm ³	5	(20)
4000-11 000/mm ³	6	(24)	50 000-100 000/mm ³	4	(16)
>11 000/mm ³	8	(32)	100 000-150 000/mm ³	9	(36)
Deranged LFTs	21	(84)	Deranged RFTs	10	(40)
AST/ALT	21	(84)	Urea >45 mg/dL	10	(40)
SALP	18	(72)	Creatinine >1.5 mg/dL	6	(24)
Abnormal chest X-ray	8	(32)	Metabolic acidosis	4	(16)
Hyponatremia	10	(40)			

LFTs: liver function tests; AST: aspartate transaminase; ALT: alanine transaminase; SALP: serum alkaline phosphatase; RFTs: renal function tests.

tats like sea shore, rice fields and semi dessert area (12). Ours being a dry area with scanty rainfall and vegetation not supportive of scrub typhus, the disease was considered a rare possibility in this region. Extensive search revealed only a few sporadic cases of scrub typhus reported from this geographical area (13). The prevalence of this disease in our patients can be attributed to their occupation, since 80% of the cases were farmers (77% males and 83% females). The disease is known to occur in agricultural workers, with exposure to environmental factors including bushes, piles of wood, domestic animals and rodents significantly associated with illness. A study in Japan reported that 44% of patients engaged in farming (14). A clean living-environment and control of rodents decreased the incidence of scrub typhus significantly among troops in China (15). Moreover, during the post monsoon season farmers are involved in extensive field activities, increasing their exposure to chigger bites. This explains the large majority of ours patients (88%) presenting from the months of July to September. Post-monsoon surge in scrub typhus has been well-documented in literature (7,8,16).

The classical case includes eschar, regional lymphadenopathy and a maculopapular rash, but these are rarely encountered at present. Eschar is a black necrotic lesion, benign in nature, found in areas where skin is thin, moist and where the clothing is tight; most commonly being the waist and ankles. It is the site of attachment of the larval mite or chigger and is the most characteristic feature of scrub typhus, seldom seen in all patients. They remain attached to the skin of the host for 36-72 hours, after which they disengage and drop off onto the ground (17). Although reported to be significantly present among Western population, it is considered less common in Southeast Asians. Eschar was present among three (12%) of our patients; over the lower limb in two and on anterior chest wall. Reports from India suggest a very low association of eschar with scrub typhus consistent with our study, although the exact reason behind this significant finding is yet to be determined (7,8,16,18).

The organism after entering the human body invades the target cells which are vascular endothelium and reticuloendothelial system. This leads to increased capillary permeabil-

ity which results in myriad clinical manifestations including rash, shock, interstitial pneumonia, hepatitis, myocarditis, hyponatremia, encephalitis and pre-renal azotemia. Infection of endothelial cells also induces pro-coagulant activity that promotes coagulation factor consumption, platelet adhesion and leukocyte emigration and may result in clinical syndrome similar to DIC. This eventually leads to multiorgan dysfunction found in 40% of our patients (19).

The most common biochemical abnormality observed was elevated liver enzymes in 84% of the patients. This finding has been consistently associated with scrub typhus, and has been the most common laboratorial abnormality reported in various studies across Indian subcontinent (18,20,21). Thrombocytopenia was present in 72% of our patients. It occur secondary to focal occlusive endangitis which causes intravascular micro thrombosis. A study from Taiwan estimated the prevalence of significant thrombocytopenia (platelet count <100 000/mm³) to be 44% (22). Although the association of thrombocytopenia is well-documented in literature, the proportion of our patients with reduced platelet counts is significant when compared with the previous studies reported from India (18,20).

CSF analyses in patients with scrub typhus are similar to viral and tubercular meningitis (23). Two of our patients had a constellation of clinical features suggestive of meningitis including headache, neck rigidity and altered sensorium. CSF examination revealed increased proteins with lymphocytic pleocytosis and both these patients improved with doxycycline therapy. Myocarditis, an uncommon manifestation of scrub typhus, has been reported in few patients (23). 12% of our patients who had nonspecific ST-T wave changes on ECG were diagnosed of myocarditis aided by echocardiography. Each of these patients presented with shock, which was characteristically unresponsive to fluid resuscitation and were eventually managed successfully with inotropic support apart from antibiotic therapy.

The tests for isolation of organism, *in vitro* cell culture and mouse inoculation, have high sensitivity and specificity but are cumbersome, taking about 5-60 days and are not routinely available (24). Hence, serological tests remain the

mainstay in scrub typhus. Immunofluorescence assay (IFA), which can be modified to detect IgM and IgG separately, is the gold standard serological test. ELISA for detection of IgM antibody, used in this study is a suitable alternative to IFA (25). The oldest test in current use is the Weil–Felix OX-K agglutination reaction, which is inexpensive, easy to perform, and results are available overnight; however, it lacks specificity and sensitivity. This test is only to be used when better tests are not available. Recently, commercial rapid detection kits like Dip-S-Ticks, scrub typhus rapid cassette test (RCT), and scrub typhus IgM and IgG rapid immunochromatographic assay (PanBio, Brisbane, Australia) and Multitest Dip-S-Ticks Scrub Recombinant Assay (Integrated Diagnostics, Baltimore, Maryland, USA) have appeared in the market but are still far from the reach of most of the developing countries like India due to their high cost (26).

Treatment of choice is doxycycline, administered 200 mg/day in two divided doses for 12-14 days. Tetracycline 25-30 mg/kg in divided doses can be used as an effective alternative. Although resistance has been reported, chloramphenicol has been used in the past (27). Other drugs that have successfully used are azithromycin, clarithromycin and rifampicin. In pregnant women, azithromycin can be safely used (28). A large majority of our patients (96%) were treated with doxycycline 100 mg bid for 12-14 days. Twenty (80%) of the patients responded dramatically with improvement in clinical symptomatology and biochemical parameters. Azithromycin, 500 mg qd, was administered to patients who failed to respond to doxycycline and showed signs of clinical deterioration (16%). Although one patient recovered completely after the addition of second antibiotic, remaining 3 (12%) went into ARDS and unfortunately succumbed to it.

Mortality rate in our study was 12%, and interestingly each of these patients succumbed to ARDS despite providing mechanical ventilation. Apart from doxycycline, there were also administered azithromycin and injectable chloramphenicol but failed to respond. Whether ARDS was part of the natural disease course or secondary to drug resistance is debatable. Although mortality rates up to 30% have been documented, various Indian studies have reported a mortality of 2-12% (18,20,21,29). Our study is in agreement with these observations from the past.

Apart from the aforementioned 25 patients, four patients had co-infection with malaria and dengue (two each). They were initially managed with anti-malarial (artesunate+clindamycin) and supportive therapy, respectively. In view of deteriorating clinical status, with high index of suspicion doxycycline was added and each of these patients showed dramatic improvement; but they were excluded from study to reduce bias, despite being positive for scrub typhus by IgM ELISA. The pregnant patient who was treated with azithromycin from the outset recovered completely without any adverse obstetrical outcome.

The strengths of this study are use of highly sensitive and specific test-ELISA (IgM antibodies) for confirming the diagnosis and exclusion of patients with co-infection to minimize the bias. Although the study had its own limitations as paired sera was not analysed for rising antibody titre, the diagnosis

can be contested since all the patients had clinical and biochemical evidence characteristic of scrub typhus and showed a dramatic recovery with antibiotic therapy.

In this study, although we have included only those patients who had a positive serology; there were about 20 patients with a negative serology, who manifested with features strongly suggestive of scrub typhus. These patients were treated with doxycycline in view of high clinical suspicion, and recovered completely within 5-7 days of treatment and were afebrile on last follow up.

To sum up, scrub typhus has “re-emerged”. The primary notion that the disease had gone into hibernation in the last few decades, appears to be a misconceived hypothesis fuelled by lack of suspicion and diagnostic incompetence. Hence, the term “re-emergence” is itself debatable. Nevertheless, it forms one the most differentials in patients of acute febrile illness presenting with thrombocytopenia, shock, deranged LFTs, renal dysfunction, ARDS and multiorgan dysfunction. Clinicians should exercise high index of suspicion, despite the absence of eschar, especially in patients who are negative for tests for malaria and dengue fever.

In a country like India, especially regions of Haryana, large majority of the population indulge in farming, which forms an integral part of daily living. It is imperative that they are educated about the prevalence of this disease and various measures they could inculcate to avoid it. Measures like wearing gumboots during fieldwork should be encouraged since it helps avoid direct contact with infected mites. They should also be advised changing clothes after work, bathing after work and changing clothes to sleep, which reduces the time of contact of mites with the body thereby reducing the risk of infection. These measures coupled with early diagnosis and treatment aborts the clinical course of the disease thus preventing the development of fatal complications.

Conflict of Interest

No conflict of interest was declared by the authors.

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