



## A study of muscle involvement in scrub typhus



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### ABSTRACT

**Objectives:** Patients with scrub typhus often complain of myalgia, but a comprehensive study on muscle dysfunction is lacking. We therefore report the clinical, electromyographic and muscle biopsy findings in patients with scrub typhus.

**Methods:** Consecutive patients with scrub typhus were included, and their clinical and laboratory findings were noted. The patients with myalgia or weakness and elevated serum creatine kinase (CK) were considered to have muscle involvement. Electromyography (EMG) and muscle biopsy were done in some patients. Patients were treated with doxycycline 200 mg daily for 7 days, and their clinical and biochemical outcome on discharge and one month were evaluated.

**Results:** 13 out of 33 (39.4%) patients had muscle involvement and their CK levels ranged between 287 and 3166 (859 ± 829) U/L. EMG revealed short duration polyphasic potentials, and muscle histopathology revealed evidence of vasculitis. There were significant correlations between severity of weakness and CK levels ( $r = -0.6$ ;  $p < 0.001$ ), platelet counts ( $r = 0.4$ ;  $p = 0.04$ ), duration of illness ( $r = -0.4$ ;  $p = 0.01$ ) and disability on discharge ( $r = -0.4$ ;  $p = 0.04$ ). Patients with muscle involvement had more severe illness evidenced by a lower Glasgow Coma Scale score ( $p < 0.001$ ), thrombocytopenia ( $p = 0.05$ ) and greater disability on discharge ( $p = 0.007$ ), when compared to those without muscle involvement. All the patients had complete recovery following doxycycline therapy, and CK levels also normalized.

**Conclusion:** Muscle dysfunction was present in 39% patients with scrub typhus. Although muscle histopathology showed evidence of vasculitis, patients responded to doxycycline.

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### 1. Introduction

Rickettsial infections are emerging infectious diseases and prevalent in most parts of the world although the organism differs in different regions. Rickettsioses are seasonal and the arthropod hosts determine their epidemiology and geographical distribution. Three taxonomic groups of rickettsial species have been described. The typhus group includes *R. typhi* (flea-borne) and *R. prowazekii* (louse-borne). The spotted fever group includes about 20 species of organisms pathogenic to humans which are mostly tick-borne and the scrub typhus group includes *Orientia tsutsugamushi* which is mite-borne. *O. tsutsugamushi* is an obligate intracellular gram negative bacterium, and was first reported from Japan in 1899. Humans are accidentally affected in this zoonotic disease. Chiggers of trombiculid mites get infected by feeding on the body fluids of small infected mammals including rodents. They remain

infected throughout their life and also transmit the infection to their progeny. Therefore, mites are the natural reservoir as well as the vector of scrub typhus. Scrub typhus is an occupational disease in the rural areas of Asia-Pacific region which is also known as “tsutsugamushi triangle”. Patients with scrub typhus usually present with an acute febrile illness and multi-organ dysfunction including pneumonia, acute renal failure, liver dysfunction, myocarditis, bleeding diathesis and meningo-encephalitis. Myalgia in scrub typhus is common, and in a study from Korea myalgia was reported in 77% patients, with elevated creatine kinase (CK) levels in 26.4% [1]. High CK levels were also reported in a patient with Rocky Mountain spotted fever who developed acute respiratory failure and eventually died. His autopsy revealed multifocal rhabdomyolysis [2].

Fever with generalized myalgia may occur in a number of viral infections including Dengue, Chikungunya, Influenza, Coxsackie and Echovirus [3–5]. Muscle dysfunction may be due to diverse pathophysiological changes ranging from viral myositis, edema and hemorrhage into the muscle, to metabolic changes resulting in transient muscle dysfunction as described in dengue [6,7]. Though myalgia is frequent in scrub typhus, its basis has not been systematically studied. In this

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communication we report the clinical, biochemical, electromyographic and muscle histology findings in patients with scrub typhus.

## 2. Materials and methods

### 2.1. Study population

This study was carried out in a tertiary care teaching hospital in North India between 2013 and 2014. Consecutive patients with scrub typhus, diagnosed on the basis of an immuno-chromatographic assay of scrub typhus antibodies and/or a positive Weil–Felix test were included. Scrub typhus patients with elevated serum CK levels along with myalgia and/or muscle weakness were considered to have muscle involvement, and were included in the present study.

### 2.2. Clinical evaluation

A clinical history including demographic information and presence of systemic manifestations including myalgia was taken. A systemic examination was done including blood pressure, skin rash, eschar, edema, lymph node enlargement, jaundice, organomegaly and rales. The presence of muscle tenderness was noted. Consciousness was assessed by the Glasgow Coma Scale (GCS). Muscle power was graded on a 0–5 Medical Research Council (MRC) scale. Muscle tone and tendon reflexes were categorized into increased, normal or reduced. Touch, pinprick, joint position sensation and co-ordination were tested when possible.

### 2.3. Investigations

Investigations included hemoglobin, blood counts, erythrocyte sedimentation rate, blood sugar, serum creatinine, blood urea nitrogen, serum bilirubin, transaminases, protein, albumin, sodium, potassium, calcium, alkaline phosphatase and CK (including MM and MB fractions). HIV serology and blood cultures were obtained, and prothrombin and activated partial thromboplastin times and international normalized ratio were also measured. A 12-lead electrocardiogram (ECG) and radiograph of the chest were carried out. Sequential Organ Failure Assessment (SOFA) scores were computed at admission using clinical and laboratory parameters.

Electromyography (EMG) was performed in patients with persisting muscle weakness when the platelet counts were more than  $40,000/\text{mm}^3$  and coagulation parameters were normal. Concentric needle electromyography (EMG) was done in muscles of the right upper and lower limbs including triceps, deltoid, extensor digitorum communis (EDC), vastus lateralis and tibialis anterior. The presence of spontaneous activity (fibrillations, positive sharp waves and complex repetitive discharges) was noted. The sizes, shapes, phases and turns of motor unit potentials (MUPs), and their interference patterns were noted. Serum CK was repeated at 7 and 15 days of admission along with platelet counts and other abnormal biochemical parameters. In 3 patients, muscle biopsy was done from the left vastus lateralis muscle, preserved in formaldehyde, and subjected to histopathological examination.

### 2.4. Outcome assessment

Outcome was defined at the time of discharge and after 1 month, based on activities of daily living (ADL) and modified Rankin Scale (mRS) scores. It was graded into complete recovery (independent and mRS scores 0, 1 and 2), partial recovery (dependent and mRS score 3) and poor recovery (bedridden and mRS scores 4 and 5) [8].

### 2.5. Statistical analysis

Clinical features, laboratory parameters (anemia, thrombocytopenia, liver or renal dysfunction) and SOFA scores were compared in patients with and without muscle dysfunction using Chi Square test for

categorical variables, and Independent *t* test or Mann–Whitney *U* test for continuous variables. In patients with muscle involvement, CK levels were correlated with day of illness, presence of hypotension, hemoglobin levels, platelet counts, serum protein, albumin, creatinine, bilirubin, transaminases and SOFA scores using Spearman or Karl–Pearson correlation tests. Variables were considered significant if the two-tailed *p* value was  $<0.05$ . The statistical analysis was done using SPSS 16 version software.

### 2.6. Standard protocol approvals, patient consents and ethical clearance

This study was performed with the approval, and in concordance with the guidelines of our Institutional Ethics Committee.

## 3. Results

### 3.1. Demography and clinical features

13 out of 33 (39.4%) patients with scrub typhus had features of muscle involvement and were included in this study. Their ages ranged between 15 and 70 (median 32) years, and 61% were males. 11 (85%) patients were from rural areas. These patients presented in the post-monsoon period between August and November. The median duration of illness prior to admission was 15 (4–30) days.

All the patients presented with an acute encephalitis syndrome (AES) characterized by fever, headache and altered sensorium. A typical eschar was seen in six patients, skin rash in three, abdominal pain in eight and bleeding diathesis in four patients (petechiae in two and gastrointestinal hemorrhage in three). Pedal edema was noted in five and hypotension in six patients. Eight patients had lymphadenopathy, three had hepatomegaly and one had splenomegaly. GCS scores ranged between 5 and 12, and four were deeply comatose (GCS score  $\leq 8$ ). One patient had respiratory distress and required mechanical ventilation for two days. Nine of these patients needed intensive care because of hypotension, multisystem dysfunction and/or deep coma. Multi-organ dysfunction (dysfunction of  $\geq 3$  organs) was present in 10 patients. Median SOFA score was 6 (range 4–12), and in 10 patients the SOFA score was 5 or more.

Thirteen patients had varying degree of quadriparesis. Muscle weakness was severe (MRC grade  $<3$ ) in nine patients, and mild (MRC grade  $\geq 3$ ) in four patients. Muscle tone was reduced in four patients, and two patients had hyporeflexia. Muscle tone and tendon reflexes were increased in four patients who were deeply comatose.

### 3.2. Investigations

All the patients were anemic (Hb  $<12$  g/dl) with low hematocrit ( $<45\%$ ). Seven patients had polymorphonuclear leucocytosis, and nine had significant thrombocytopenia ( $<100,000/\text{mm}^3$ ). Two patients had raised serum creatinine ( $>1.6$  mg/dl), four had hypokalemia ( $<3.5$  mEq/L) and two had hyponatremia ( $<136$  mEq/L). All the patients had liver dysfunction with elevated transaminases, but serum bilirubin was elevated ( $>1.3$  mg/dl) in 3 patients only. Five patients had coagulopathy and D-dimer was positive in seven. Serum albumin was low ( $<3.5$  g/dl) in 10 patients, and albuminuria was present in 12, which was associated with urinary sediments in three. Chest radiograph revealed infiltrates suggestive of pneumonia in eight patients.

### 3.3. Muscle involvement

In the 13 patients with muscle involvement, median CK level was 453 (287–3166) U/L, and the MM fraction was elevated in all (median 438, range 263–3112 U/L). Patients with muscle involvement had significantly lower GCS scores ( $p < 0.001$ ), lower platelet counts ( $p = 0.05$ ) and greater disability on discharge ( $p = 0.007$ ) compared to those without muscle involvement (Table 1). The serum CK levels

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