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Neurological manifestations of scrub typhus in a tertiary care hospital in India

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Abstract:

This research focuses on the neurological symptoms of scrub typhus; early diagnosis is important to enable timely medical intervention and improve outcomes. Therefore, it is of interest to evaluate patients with laboratory-confirmed scrub typhus and neurological manifestations at a tertiary care teaching hospital. Demographics, clinical information, laboratory results, CSF analysis, neuroimaging and treatment outcomes were collected and analyzed descriptively. Five patients with neurological manifestations of scrub typhus were evaluated, including peripheral motor axonal neuropathy, ischemic stroke and meningoencephalitis, with CSF and electrophysiological findings supporting the neurological diagnoses. Patients improved after doxycycline treatment and corticosteroids were given to those with severe neurological involvement.

Keywords: Acute febrile illness, cerebral infarction, meningoencephalitis, neurological manifestations, scrub typhus

Background:

Scrub typhus is a rickettsial infection caused by *Orientia tsutsugamushi*, which is a Gram-negative obligate intracellular coccobacillus that is transmitted to humans by the bite of the larval stage (chigger) of the trombiculid mite. The bites of these chiggers leave the characteristic "eschar," which is pathognomonic of scrub typhus [1, 2]. The disease has been reported worldwide, but it is endemic in the *tsutsugamushi* triangle, a geographical region comprising South and East Asia and the Southwest Pacific. In India, studies have shown the endemic nature of scrub typhus in many states and union territories. Scrub typhus is an important cause of acute febrile illness in India [3, 4]. The case fatality rate may be as high as 30% if left untreated [5]. Scrub typhus is grossly underdiagnosed in India due to its non-specific clinical presentation, limited awareness, low index of suspicion among clinicians and a lack of diagnostic facilities. Infection manifests clinically as a non-specific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhoea and breathlessness and ranges to severe multi-organ dysfunction [6]. Central nervous system (CNS) involvement is a known complication of scrub typhus, which ranges from aseptic meningitis to frank meningoencephalitis [7]. Various neurological manifestations include meningoencephalitis, meningitis, encephalitis, encephalopathy, seizure, myelitis, ADEM, cranial neuropathies like sixth, seventh, mononeuritis multiplex, brachial plexopathy, Guillain-Barré syndrome and rarely stroke. The most common reported manifestation is meningoencephalitis [8, 9]. Therefore, it is of interest to evaluate the diverse neurological manifestations of scrub typhus, emphasizing that early diagnosis and prompt treatment are associated with favourable outcomes.

Materials and Methods:

This retrospective study was conducted at a tertiary care teaching hospital. Medical records of patients with laboratory-confirmed scrub typhus who developed neurological manifestations were reviewed. Diagnosis was established based on compatible clinical features and positive serological testing for *Orientia tsutsugamushi*, in accordance with institutional protocol. Demographic, clinical, laboratory, cerebrospinal fluid, neuroimaging, treatment and outcome data were extracted from

patient records. Neurological manifestations were classified based on clinical evaluation and relevant investigations. Data were analyzed descriptively and presented as frequencies, percentages, or summary statistics where appropriate. Institutional Ethics Committee approval was obtained and patient confidentiality was maintained throughout the study.

Results:

Five patients with scrub typhus presenting with neurological manifestations were evaluated. Neurological complications included peripheral neuropathy, ischemic stroke and meningoencephalitis. Electrophysiological findings and clinical outcomes are summarized below (Table 1). Case 1 is a 41-year-old male who underwent electromyography (EMG), motor nerve conduction studies (MNCS), and sensory nerve conduction studies (SNCS) and F-wave latency assessments of both upper and lower limbs. The study showed mild prolongation of tibial F-wave latencies, raising suspicion for early Guillain-Barré syndrome (GBS). The patient showed clinical improvement following treatment with doxycycline and an adjunctive corticosteroid. Case 2 patient presented with scrub typhus-associated cerebral vasculitis complicated by ischemic stroke. In cases 3, 4 and 5, EMG/NCS evaluations in a 74-year-old female, a 56-year-old male and a 78-year-old male showed motor axonal neuropathy involving both lower limbs, with abnormalities affecting the peroneal/tibial motor nerves and on F-wave studies, with comparatively less prominent sensory nerve involvement. All patients initially presented with acute febrile illness followed by neurological manifestations, including altered sensorium, limb weakness, or focal neurological deficits. Cerebrospinal fluid examination in patients with neuropathy demonstrated elevated protein levels with minimal pleocytosis, consistent with albuminocytological dissociation suggestive of GBS. Systemic manifestations included thrombocytopenia, elevated liver enzymes and renal dysfunction in several patients. Figure 1 shows a characteristic scrub typhus eschar over the chest wall, appearing as a black necrotic crust with minimal surrounding inflammation. Peripheral neuropathy was the most frequent complication, occurring in three patients (50%), followed by ischemic stroke in two patients (33.3%), while meningitis/encephalitis occurred in one patient (16.7%). All

patients responded favourably to early doxycycline therapy and those with severe neurological involvement also improved following adjunctive corticosteroid administration.

Table 1: Cases of Scrub typhus

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Sex	41/M	44/M	74/F	56/M	78/M
Risk Factors	Chronic alcoholism	Not specified	Recent vaccination, dog bite	Bronchial asthma	Diabetes, alcohol, smoking
Presenting Complaint	Acute bilateral LL weakness for 3 days	Fever, sudden hemiparesis, slurred speech	Progressive LL weakness for 6 days	Fever for 13 days, altered sensorium	Fever, headache, altered sensorium
Fever	Present	Present	Present (brief)	High-grade prolonged	Present
Eschar	Absent	Present	Absent	Present	Absent
Neurological Features	Areflexia, motor weakness	Left hemiparesis, UMN facial palsy	Areflexia, motor weakness	Stupor, meningeal signs, stroke, neuropathy	Meningoencephalitis features and seizures
Meningeal Signs	Absent	Absent	Absent	Present	Present initially on the first day of admission
Motor Power	2/5 LL	Reduced (left side)	4/5 LL	Variable, later LL weakness	Mild to moderate reduction
Reflexes	Absent	Exaggerated	Absent	Absent LL (later)	Variable
Sensory Involvement	Absent	Absent	Absent	Not significant	Not significant
CSF Findings	Normal	Not done	Increased Protein, pleocytosis	Lymphocytic meningitis, high protein levels	Lymphocytic meningitis
MRI Brain	Normal	Right MCA infarct	Normal	Initially normal and later infarcts	Features of encephalitis
NCS Findings	Motor axonal neuropathy	Not done	Motor axonal polyneuropathy	Motor axonal neuropathy	Not done
Scrub Typhus Test	IgM positive	IgM positive	IgM & IgG positive	IgM positive	IgM positive
Final Diagnosis	AMAN variant neuropathy	Ischemic stroke (MCA thrombosis)	GBS-like motor neuropathy	Scrub typhus vasculitis with stroke	Scrub typhus meningoencephalitis
Treatment	Doxycycline, steroids and physiotherapy	Doxycycline and stroke management	Doxycycline	Doxycycline, steroids and anticoagulation	Doxycycline and supportive care
Outcome	Improved	Gradual recovery	Improved	Significant recovery	Improved

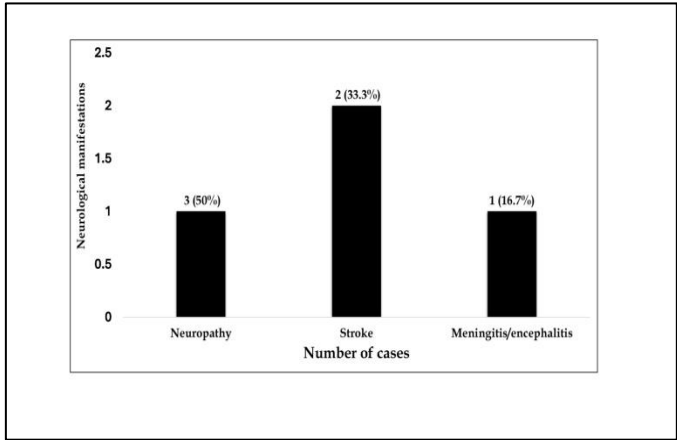


Figure 1: Cases with neurological manifestations

Discussion:

Cerebrovascular complications in scrub typhus are uncommon but have been reported secondary to vasculitis, endothelial injury and thrombotic occlusion of cerebral vessels [10]. The organism's vascular tropism leads to diffuse inflammatory damage, capillary leaks and microvascular thrombosis, predisposing susceptible individuals to ischemic complications [11]. Scrub typhus, caused by *Orientia tsutsugamushi*, is an important re-emerging rickettsial infection in tropical regions, particularly within the “*tsutsugamushi* triangle,” which includes India. Although classically presenting as an acute febrile illness, neurological involvement is increasingly

recognized and contributes significantly to morbidity and mortality [12]. Neurological manifestations range from mild aseptic meningitis to severe meningoencephalitis, myelitis, stroke, acute disseminated encephalomyelitis (ADEM), cranial neuropathies and Guillain-Barré syndrome (GBS)-like presentations [13, 14]. Figure 1 shows the distribution of neurological manifestations among the reported cases. Neuropathy was the most common manifestation, occurring in 3 cases (50%). Stroke was reported in 2 cases (33.3%). Meningitis/encephalitis was the least common, observed in 1 case (16.7%). Overall, neuropathy accounted for half of all neurological manifestations, while stroke and meningitis/encephalitis were less frequent. In the present study, all patients are presented with fever followed by neurological manifestations such as altered sensorium, limb weakness, or focal neurological deficits. Meningoencephalitis was the most common presentation, consistent with previous reports identifying it as the predominant neurological complication of scrub typhus [11, 1]. The organism causes systemic vasculitis and perivasculitis involving small blood vessels, leading to endothelial dysfunction and inflammatory injury within the central nervous system [12]. Two of our patients showed acute motor weakness with nerve conduction studies suggestive of motor axonal neuropathy. Cerebrospinal fluid analysis in these patients showed elevated protein with minimal cellular response, suggestive of albumin cytological dissociation. Such findings support an immune-mediated peripheral neuropathy, such as GBS. Molecular mimicry triggered by *Orientia tsutsugamushi* has been proposed as a mechanism for peripheral nerve involvement [1]. Similar GBS-like presentations associated with scrub typhus have been described in earlier studies [9]. One patient developed ischemic stroke with right middle cerebral artery infarction, while another showed evolving cerebral

infarcts during illness. Cerebrovascular complications in scrub typhus are uncommon but have been reported secondary to vasculitis, endothelial injury and thrombotic occlusion of cerebral vessels [13]. The organism's vascular tropism leads to diffuse inflammatory damage, capillary leakage and microvascular thrombosis, predisposing susceptible individuals to ischemic complications [14]. Systemic manifestations such as thrombocytopenia, elevated liver enzymes and renal dysfunction were observed in several patients. These findings reflect widespread endothelial injury and multi-organ involvement, which are characteristic of severe scrub typhus infection [12]. Advanced age, diabetes mellitus, alcoholism and other comorbidities appeared to be associated with more severe disease in our patients, like findings from previous studies [15-19]. Eschar, although considered pathognomonic, was present only in a minority of cases. Previous Indian studies have also reported inconsistent detection of eschar, limiting its usefulness as a diagnostic marker in endemic regions [18-19]. Therefore, a high index of clinical suspicion is essential in patients presenting with acute febrile illness and neurological symptoms, even in the absence of eschar. All patients improved with early doxycycline therapy and supportive care. Prompt antimicrobial treatment remains the cornerstone of management and significantly reduces complications and mortality [10]. Patients with severe neurological involvement, particularly vasculitic complications and rapidly progressive deficits, also showed clinical improvement following adjunctive corticosteroid therapy. Steroids may help reduce immune-mediated inflammation and endothelial injury in severe scrub typhus. Early recognition and prompt initiation of doxycycline, with selective use of corticosteroids in severe neurological manifestations, are crucial to prevent complications, reduce morbidity and improve neurological recovery. This study extends the knowledge of scrub typhus by emphasizing its atypical neurological symptoms, apart from the classical meningoencephalitis. It highlights the importance of considering scrub typhus in a patient with acute febrile illness, particularly if the patient has any neurological symptoms such as focal deficits, seizures, cerebrovascular events or peripheral neuropathies, without any apparent cause. Early recognition, accurate diagnosis and timely antibiotic treatment are important for limiting neurological complications and achieving good outcomes.

Conclusion:

Scrub typhus can present with diverse neurological manifestations ranging from meningoencephalitis to immune-mediated neuropathies and cerebrovascular complications, often posing diagnostic challenges. Early clinical suspicion is essential, especially

in endemic regions and in the absence of eschar. Prompt initiation of doxycycline significantly improves outcomes, while adjunctive corticosteroid therapy is beneficial in selected patients with severe inflammatory neurological involvement.

Conflict of interest: Nil

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