

# Neurological Manifestations of Scrub Typhus: A Case Series from Tertiary Care Hospital in Southern East Rajasthan

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## Abstract

Scrub typhus is an acute febrile infectious illness caused by rickettsia species *Orientia tsutsugamushi*. In recent years, scrub typhus has reemerged as a life-threatening disease in India. Scrub typhus has diverse clinical manifestations ranging from a nonspecific febrile illness to severe multiorgan dysfunction, and neurological complications are also common. Spectrum of neurological complications varies from common complications such as aseptic meningitis, meningoencephalitis and cerebellitis to rare complications such as myelitis, cerebral hemorrhage, acute disseminated encephalomyelitis (ADEM), and cerebral infarction. Scrub typhus is not a common cause of acute febrile illness in state like Rajasthan, but has emerged as a life-threatening disease in recent years along with dreaded neurological complications. This case series highlights various neurological manifestations of scrub typhus as early diagnosis and treatment of neurological complications have good prognosis.

**Keywords:** Acute febrile illness, cerebellar signs, neurological manifestations, scrub typhus

## INTRODUCTION

Scrub typhus is a rickettsial infection caused by *Orientia tsutsugamushi*, which is a Gram-negative obligate intracellular coccobacillus that is transmitted to the humans by the bite of larval stage (chigger) of trombiculid mite. The bites of these chiggers leave the characteristic “eschar,” which is pathognomonic of scrub typhus.<sup>[1,2]</sup> The characteristic eschar is seen in 40%–50% of patients and may be inconspicuous as it is often present in areas like groin, gluteal folds, breast folds, and external genitalia and may go unnoticed in dark-skinned people.<sup>[3]</sup>

The disease has been reported from all over the world, but it is endemic in terrains of the tsutsugamushi triangle, a geographical region comprising South and East Asia and the Southwest Pacific.<sup>[4]</sup>

In India, studies have shown the endemic nature of scrub typhus in many states and union territories. The first reported cases were from Himachal Pradesh.<sup>[3]</sup> Scrub typhus is an important cause of acute febrile illness in India.<sup>[4]</sup> Case fatality rate may be as high as 30% if left untreated.<sup>[5]</sup> Scrub typhus is grossly underdiagnosed in India due to its nonspecific clinical presentation, limited awareness, and low index of suspicion among clinicians and lack of diagnostic facilities.<sup>[6]</sup> Infection manifests clinically as a nonspecific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhea, and breathlessness and ranges to severe multiorgan dysfunction.<sup>[6]</sup>

Central nervous system (CNS) involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis.<sup>[7]</sup>

Various neurological manifestations include meningoencephalitis, meningitis, encephalitis, encephalopathy, seizure, myelitis, ADEM, cranial neuropathies like sixth, seventh, mononeuritis multiplex, brachial plexopathy, Guillain–Barre syndrome, and rarely stroke. The most common reported manifestation is meningoencephalitis.<sup>[1,8,9]</sup>

Here, we report a case series of five cases of scrub typhus presenting in the neurology department with various neurological manifestations [Table 1].

## DISCUSSION

Scrub typhus was endemic in India in the past decade especially in Himachal, UP, and some states of south India, but since the past few years scrub typhus is emerging as a life-threatening illness in other parts of India. Scrub typhus is uncommon in Rajasthan, but in our region due to abundant paddy fields in rural area, scrub typhus is emerging as an important cause of acute febrile illness in recent years. This disease is common in farmers and villagers of our region. Previous studies that were published

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**Table 1: Clinical profile of scrub typhus patients with neurological manifestations**

	Case 1	Case 2	Case3	Case 4	Case 5
Age (years)	65	48	17	21	10
Sex	Female	Female	Male	Male	Male
Living status	Rural	Rural	Urban	Rural	Rural
Presenting complaints	Fever, altered sensorium, difficulty in respiration	Fever, irritable behavior, urinary incontinence	High-grade fever, throbbing headache, periorbital pain	Headache, vomiting, difficulty in respiration, altered sensorium	Fever, headache, vertigo, diplopia, speech difficulty
Extraneurological signs	Lung crepitations +	-	-	Lung crepitations +, tachycardia, hypotension	-
Neurological signs	Neck rigidity + bilateral plantar-flexor	Disorientation, DTR-exaggerated, bilateral plantar-extensor	-	Bilateral plantar-extensor	Bilateral 6 cranial nerve palsy, papilledema in both eyes, scanning speech, dysdiadochokinesia, ataxic gait
Eschar	Absent	Absent	Absent	Absent	Absent
Hematological parameters					
Scrub typhus IgM ELISA	+	+	+	+	+
HIV	-	-	-	-	-
HbsAg					
Anti-HCV AB					
M.P.	-	-	-	-	-
Dengue-ELISA IgM widal					
TLC (cells/mm <sup>3</sup> )	11,800	8400	13,500	12,400	10,450
S. urea (mg/dL)	108	40	32	88	26
S. creatinine	1.9	1.2	0.9	2.2	1.0
S. bilirubin (mg/dL)	1.8	2	0.8	2.3	0.9
SGOT	48	110	35	120	55
SGPT	44	123	22	203	40
S. vitamin B12 (pg/mL)			296		
ANA			-		
APLA			-		
Homocystine			15.2 units		
CSF findings					
Cells (/mm <sup>3</sup> )	6	20		2	5
Protein (mg/dL)	81	64		57	91
Sugar (mg/dL)	42	61		51	45
ZN stain	-	-		-	-
India Ink	-	-		-	-
MRI/MR venogram	MRI brain - normal	Bilateral frontotemporoparietal cortical white matter hyperintensity on T2W and FLAIR image [Figure 1a], DW images shows restriction in same area	T2 and FLAIR images - white matter edema in bilateral high frontoparietal region, MR Venogram showed acute thrombus in superior saggital sinus [Figure 1b]	MRI brain T2W and FLAIR sequences showed hyperintensity in medulla and pontomedullary junction [Figure 1c]	T2W and FLAIR sequences showed hyperintensity in brainstem, cerebellum and periventricular region
Probable neurological diagnosis	Meningoencephalitis	ADEM	Cerebral venous sinus thrombosis	Meningoencephalitis	ADEM
Treatment	Azithromycin, doxycycline, steroids	Azithromycin, doxycycline, steroids	Azithromycin, doxycycline, LMWH, nicoumalone	Pipercillin tazobactam, azithromycin, steroids	Azithromycin, doxycycline, steroids

*Contd...*

Table 1: Contd...

	Case 1	Case 2	Case3	Case 4	Case 5
Outcome	Death	Complete recovery in a week	Significant improvement within a week	Significant improvement within 2 weeks	Partial recovery in a week

DTR: Deep tendon reflex; TLC: Total leukocyte count; HIV: Human immunodeficiency virus; MP: Malarial parasite antigen; HCVAB: Hepatitis C virus antibody; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ANA: Antinuclear antibody; APLA: Antiphospholipid antigen; CSF: Cerebrospinal fluid; ELISA: Enzyme linked immunosorbent assay; MRI: Magnetic resonance imaging; MRV: Magnetic resonance venogram; T2W: T2-weighted; FLAIR: Fluid attenuated inversion recovery; ADEM: Acute demyelinating encephalomyelitis



**Figure 1:** FLAIR MRI images shows (a) bilateral frontotemporoparietal cortical white matter hyperintensity; (b) acute thrombus in superior sagittal sinus; (c) hyperintensity in medulla and pontomedullary junction

reported cases of scrub typhus and their outcome from states like Himachal Pradesh, Uttar Pradesh, and Pondicherry; this is the first case series reported from western state Rajasthan with extensive work up and showing importance of early diagnosis and treatment. All cases of scrub typhus included in this case series had four fold rise in antibody titer on ELISA IgM test. Malaria and dengue are also a common cause of acute febrile illness in our region so both these two and other causes of infectious and noninfectious ruled out by various laboratory test.

Nervous system involvement is a common complication of scrub typhus infection. *Orientia tsutsugamushi* enters the CNS by invasion of endothelial cells in blood vessels. Cytokines released by acutely inflamed vascular endothelial cells secondary to invasion in blood vessels damage endothelial integrity causing fluid leakage. There is localized platelet aggregation, polymorphs, and monocyte proliferation, leading to angiitis.<sup>[1,8]</sup> CNS involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis.<sup>[7]</sup> Many studies in India and in other countries found that meningoencephalitis is a most common neurological complication of scrub typhus. A study done by Rana *et al.* found that the most common neurological manifestation was meningoencephalitis (40%).<sup>[8]</sup> A cross-sectional study on 37 patients published by Mishra *et al.* found two-thirds of patients with scrub typhus had neurological involvement manifesting as meningoencephalitis, encephalitis, or encephalopathy,<sup>[1]</sup> but cerebrospinal fluid findings can mimic tuberculous meningitis and viral meningoencephalitis.<sup>[7]</sup> In a Korean study, 89 patients with severe complications and 119 without severe complications due to scrub typhus were evaluated. In the group with severe scrub typhus, 23 (11.3%) patients had meningoencephalitis.<sup>[10]</sup> Scrub typhus as a cause of ADEM is extremely rare, pathophysiology is obscure, but it

has been postulated to result from an autoimmune response to myelin basic protein triggered by infection as in our cases it may be due to cross reactivity of IgM antibodies to myelin protein.<sup>[11]</sup>

Meningoencephalitis was the most common encountered symptom in our study along with rare complications such as ADEM and cerebral venous thrombosis. We started early and prompt treatment to prevent further complications and promote early recovery; despite that, one patient died due respiratory failure secondary to scrub typhus.

## CONCLUSION

This case series highlights that scrub typhus is emerging as a life-threatening disease in southeast Rajasthan. Neurological manifestations are very common in scrub typhus. Knowledge of these manifestations will enable clinicians to consider scrub typhus as one of the differential diagnoses of acute febrile illness with neurological involvement. The neurological complications in scrub typhus have good prognosis if diagnosed and treated early.

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## Conflicts of interest

There are no conflicts of interest.

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