Case Series

Clinical spectrum of uncommon neurological manifestations in scrub typhus: A rural Indian case series

Jitu VT, Bency MB

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Abstract

Scrub typhus, caused by *Orientia tsutsugamushi*, is a re-emerging zoonotic infection endemic to the Asia-Pacific region including India. It presents with diverse and often nonspecific clinical manifestations, making diagnosis a challenge . We present three serologically (IgM ELISA) confirmed cases of scrub typhus from rural Tamil Nadu, India, that exhibited distinct neurological symptoms. Case 1: A 56-year-old male farmer with meningoencephalitis characterised by altered sensorium, neck rigidity, and papilloedema, who achieved complete recovery with doxycycline. Case 2: A 45-year-old woman with acute inflammatory myopathy, severe proximal muscle weakness, and elevated muscle enzymes, requiring combined doxycycline and steroid therapy for full recovery. Case 3: a 39-year-old female rice mill worker who developed bilateral moderately severe sensorineural hearing loss with vestibular symptoms, partially improving with doxycycline. These cases highlight the diverse neurological manifestations of scrub typhus beyond classical presentations, advocating for heightened clinical awareness to reduce morbidity from this re-emerging tropical disease.

Keywords: *Scrub typhus, Orientia tsutsugamushi, India, Doxycycline, Myositis, Meningoencephalitis, Sensorineural hearing loss*

Introduction

Scrub typhus, a febrile illness caused by the obligate intracellular bacterium *Orientia tsutsugamushi*, is a significant public health concern, particularly in the Asia-Pacific region. The World Health Organisation (WHO) estimates that nearly one billion people are at risk, with over one million new cases reported annually, contributing to up to 50% of acute febrile illness hospitalisations in the endemic "Tsutsugamushi Triangle" spanning from Japan to Australia and

[1]*Department of General Medicine, Shri Sathya Sai Medical College &Research Institute, Sri Balaji Vidyapeeth Deemed-to-be University, Pondicherry, India*
[2]*Department of Audiology & Speech Language Pathology, Shri Sathya Sai Medical College &Research Institute, Sri Balaji Vidyapeeth Deemed-to-be University, Pondicherry, India*

Address for correspondence: Dr. Jitu V Thomas; Tel: +91 9961744085: Email:jituvthomas@gmail.com;

https://orcid.org/0009-0006-3138-8476

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Pakistan., Scrub typhus is increasingly recognised in India , with a high prevalence in Tamil Nadu, where agricultural labourers are particularly susceptible due to environmental exposure to infected trombiculid mites (*Leptotrombidium delicense*).[1,2]

While classical scrub typhus presents with fever, headache, myalgia, a maculopapular rash (present in 30-50% of cases), and a characteristic eschar at the chigger bite site, its clinical spectrum is remarkably diverse and often mimics other tropical infections. Neurological involvement, occurring in 10-30% of cases, represents a serious complication that can significantly impact patient morbidity and mortality.[3] These manifestations range from mild headaches and neck stiffness to severe conditions, such as meningoencephalitis, acute disseminated encephalomyelitis, cranial nerve palsies, and even sensorineural hearing loss. The pathophysiology often involves direct vascular injury, immune-mediated mechanisms, or both, leading to diverse presentations.
Clinical and laboratory diagnosis of scrub typhus remains challenging due to non-specific symptoms such as the absence of an eschar in many cases (reported in only 20.8% of cases) and limited access to specific diagnostic tests in rural settings. Although the Weil-Felix test is a rapid screening tool, its sensitivity (55-70%) and specificity (30-60%) are low, limiting its diagnostic utility. Immunofluorescence assay (IFA) is the gold standard, but IgM ELISA (specificity of 82-94%and sensitivity of 78-88%) is widely used due to its practicality and availability. Early recognition and prompt doxycycline treatment are vital for favourable outcomes and to prevent long-term neurological sequelae.[4]

Despite growing awareness, atypical neurological manifestations, such as isolated myositis and sensorineural hearing loss, are often underreported leading to diagnostic delays and potentially adverse patient outcomes. This case series aims to enhance clinical understanding by detailing three distinct and atypical neurological presentations of scrub typhus from rural Tamil Nadu, thereby emphasising the need for a high index of suspicion in endemic areas.

We present three cases of scrub typhus with diverse neurological manifestations managed at a rural tertiary care centre in Tamil Nadu, India. All patients provided informed consent for the publication of clinical details.

Case 1: Scrub typhus meningoencephalitis

A 56-year-old male farmer presented with a 5-day history of high-grade fever, headache, vomiting and progressively altered sensorium. He had a history of hypertension and smoking. On examination, he was febrile (39.4 °C), hypertensive (168/98 mmHg), disoriented, and exhibited terminal neck rigidity and bilateral papilledema but no eschar or rash. The cranial nerves and other systemic examinations were normal.

Laboratory investigations revealed leukocytosis (TLC 13.4 × 10^9/L with 85% polymorphs, platelet count 145 × 10^9/L) and elevated liver transaminases (ALT 99 U/L, AST 88 U/L, GGT 310 U/L, and ALP 314 U/L). Renal function and chest radiography findings were normal. Abdominal ultrasonography revealed mild hepatosplenomegaly. Cerebrospinal fluid (CSF) analysis revealed glucose 48 mg/dL, protein 82 mg/dL, and 202 cells/cu mm with lymphocytic predominance, negative for acid-fast bacilli, viral antibodies (Herpes simplex, Japanese encephalitis), adenosine deaminase, and GeneXpert. The non-contrast CT of the head was unremarkable. Scrub typhus IgM was positive (value 1.15, normal <0.14).

He was treated with intravenous doxycycline (100 mg twice daily for 3 days, followed by oral doxycycline for 4 days), mannitol, and levetiracetam. His sensorium improved significantly by day 3, and he became afebrile and asymptomatic by day 7 of the antibiotic therapy. A follow-up CSF study after recovery was also normal. The patient was discharged on day 10 with complete resolution of symptoms.

Case 2: Acute myopathy as an atypical presentation

A 45-year-old woman presented with 5 days of fever, cough, vomiting, generalised body aches and progressive increase in pain involving bilateral thigh and calf muscles leading to proximal muscle weakness. The patient was conscious, alert and oriented. Examination revealed fever (38.9 °C), heart rate 90 beats/min, BP 100/70 mmHg, no rash but a characteristic eschar on the left groin (Figure 1), confirming the diagnosis. Neurological examination showed significant muscle tenderness, especially in the proximal lower limb muscles, with reduced motor power (mMRC grade 3-/5 proximally, 3+/5 distally), sparing the neck muscles.

Figure 1: Eschar on left groin

Blood tests showed leukocytosis (TLC 16.4 × 10⁹/L with 87% polymorphs, platelet count 152 × 10⁹/L). Liver, renal, and thyroid function tests were all normal. Serological tests for malaria, dengue, Japanese encephalitis, typhoid, Borrelia, Chikungunya, COVID-19, and hepatitis B/C were negative. The scrub typhus IgM ELISA was positive (value 1.28, normal <0.14). Inflammatory markers (CRP 96 mg/L, normal <10 mg/L and ESR 82 mm/hr, normal <20 mm/hr) and serum muscle enzymes (CPK 1,842 U/L, normal <200 U/L, aldolase 28 U/L, normal <7.6 U/L, and LDH 612 U/L, normal <250 U/L) were significantly elevated. Autoimmune and connective tissue panels, including those for myositis-specific autoantibodies, were negative. Electromyography revealed a myopathic pattern.

The patient was initially treated with intravenous doxycycline (200 mg/day for five days), followed by oral doxycycline (100 mg twice daily) for another five days. Although fever and myalgia improved within 3 days, muscle weakness persisted. She was treated with intravenous methylprednisolone (500 mg daily for five days), after which her muscle weakness resolved. The patient was discharged on day 12 with no neurological deficits. The follow-up was uneventful.

Case 3: Sensorineural hearing loss (SNHL)

A 39-year-old healthy female rice mill worker presented with 4 days of fever, chills, rigor, myalgia, reduced hearing, tinnitus, and dizziness, with hearing symptoms developing on day 3 of fever. The patient denied otalgia, ear discharge, ear trauma, or ototoxic drug use. Examination showed fever (38.3 °C), heart rate 86 beats/min, BP 110/70 mmHg, and orthostatic hypotension (supine BP 110/70 mmHg and standing 90/60 mmHg). She was dehydrated, with dry mucous membranes and prolonged capillary refill time, but no rash or eschar was found. Neurological examination was normal, except for Weber's test centralisation and a positive Rinne's test bilaterally with decreased air-bone conduction.

The initial diagnosis was acute vestibular neuritis. Audiological evaluation by an audiologist revealed bilateral moderately severe to severe SNHL on pure tone audiometry and absent reflexes on impedance audiometry (Figure 2).

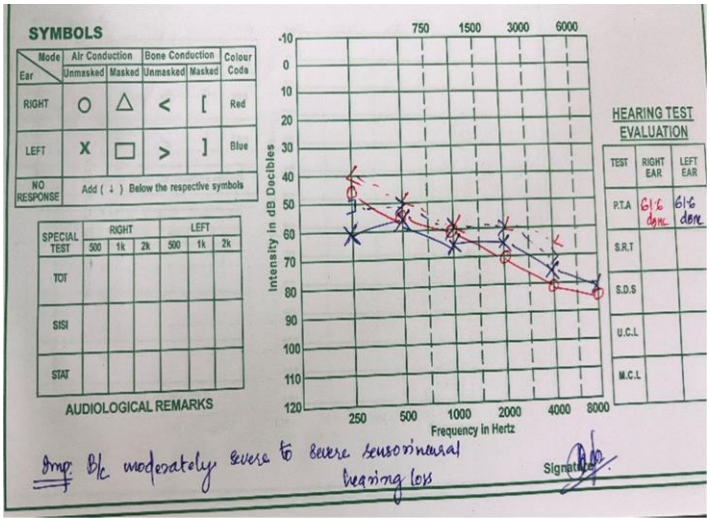

Figure 2: Audiogram of the patient

Blood tests showed elevated leukocyte counts (15.2 × 10^9/L with 80% neutrophils) and normal haemoglobin and platelet count (168 × 10^9/L). Liver function tests showed elevated (ALT 112U/L, AST 48U/L, GGT (230 U/L), and ALP (290 U/L). Renal function was also impaired. Ultrasound scan of the abdomen showed mild hepatosplenomegaly. On day 3, she developed hemodynamic instability and was moved to critical care due to metabolic acidosis (ABG) and elevated procalcitonin (34 ng/mL), suggestive of sepsis. She was started on empirical intravenous ceftriaxone and intravenous fluids. Blood and urine cultures were negative for pathogens. The Leptospira IgM test was negative, but the scrub typhus IgM test was positive (value 1.42, normal <0.14).

With a diagnosis of scrub typhus presenting with acute febrile illness and bilateral SNHL, she was started on intravenous doxycycline (100 mg twice daily) on day 3. Her fever subsided, her blood pressure stabilised, and she was stepped down to oral doxycycline (100 mg twice daily) and moved back to the ward on day 5. Repeat audiometry on day 8 revealed improvement. She was discharged on day 14 and showed marginal improvement in hearing impairment at the one-month follow-up.

A summary of the 3 cases is provided in Table 1.

Table 1: Summary of clinical features, diagnostics, and outcomes of scrub typhus cases

Feature	Case 1: Meningoencephalitis	Case 2: Acute myopathy	Case 3: Sensorineural hearing loss (SNHL)
Age/Sex	56/Male	45/Female	39/Female
Occupation	Farmer	Housewife	Rice Mill Worker
Presenting complaints	Fever, headache, vomiting, altered sensorium	Fever, cough, vomiting, myalgia, proximal weakness	Fever, chills, rigor, myalgia, reduced hearing, tinnitus, dizziness
Duration of symptoms	5 days	5 days	4 days
Eschar	Absent	Present (left groin)	Absent
Neurological findings	Altered sensorium, neck rigidity, bilateral papilledema	Proximal muscle weakness (mMRC 3-/5), muscle tenderness	Bilateral moderately severe SNHL, vestibular symptoms
CSF analysis	Lymphocytic pleocytosis, elevated protein	Not applicable	Not applicable
Imaging	CT head normal	Not applicable	Not applicable
Serology (IgM ELISA)	Positive	Positive	Positive
Other key labs	Leukocytosis, elevated LFTs, thrombocytopenia	Leukocytosis, elevated, CPK, aldolase, LDH, normal platelet counts	Leukocytosis, elevated LFTs, impaired RFTs, metabolic acidosis, elevated procalcitonin, normal platelet counts
Treatment	IV Doxycycline, Mannitol, Levetiracetam	IV Doxycycline, IV Methylprednisolone	IV Doxycycline, IV Ceftriaxone, IV fluids
Outcome	Complete recovery	Complete recovery	Partial improvement in hearing
Hospital Stay	10 days	12 days	14 days

CSF, cerebrospinal fluid; CPK, creatine phosphokinase; CT, computed tomography; IgM ELISA, immunoglobulin M enzyme-linked immunosorbent assay; IV, intravenous; LDH, lactate dehydrogenase; LFTs, liver function tests; mMRC, modified Medical Research Council; RFTs, renal function tests; SNHL, sensorineural hearing loss.

Discussion

This case series from rural Tamil Nadu illustrates the diverse and often atypical neurological manifestations of scrub typhus, underscoring the significant diagnostic challenge it poses in endemic regions. The three cases presented with meningoencephalitis, acute inflammatory myopathy, and sensorineural hearing loss, all confirmed serologically, highlighting the protean nature of this re-emerging tropical disease.

Meningoencephalitis (case1): This is the most common neurological complication of scrub typhus, affecting 10-30% of cases. The pathogenesis involves direct invasion of the central nervous system by *O. tsutsugamushi* and immune-mediated vasculitis.[5] The CSF findings of lymphocytic pleocytosis and elevated protein levels are consistent with previous reports of scrub typhus meningoencephalitis. While CT scans are normal early on, the CSF findings of lymphocytic pleocytosis and elevated protein levels are consistent with previous reports of scrub typhus meningoencephalitis. A normal CT scan in the early stages is also a recognized feature, with MRI showing superior sensitivity for subtle parenchymal changes.[6] Prompt doxycycline therapy led to complete clinical and biochemical recovery, emphasising the critical role of early treatment in preventing prolonged neurological sequelae and reducing mortality.[7,8]

Acute inflammatory myopathy (case 2) is a rare manifestation. While myalgia is common in scrub typhus (reported in 77% of cases), profound muscle weakness with markedly elevated

muscle enzymes and myopathic electromyography patterns are uncommon.[9] The presence of an eschar in our patient (case 2) was a crucial diagnostic clue. The proposed mechanisms of muscle dysfunction include direct bacterial invasion, immune-mediated myositis, microvascular injury and the release of circulating cytokines or mycotoxins.[10] Our successful use of methylprednisolone alongside doxycycline in this severe presentation suggests an immune-mediated mechanism, possibly driven by an exaggerated host immune response to the pathogen rather than direct bacterial invasion. This is an approach increasingly advocated in severe cases with significant inflammatory responses, although controlled studies are needed. This case differs from primary inflammatory myopathies by negative autoimmune panels and the presence of eschar.

Bilateral SNHL (case 3) is a particularly rare and often under-recognised complication of scrub typhus. Auditory disturbances, including otalgia and tinnitus, typically occur during the second week of illness.[11] Similar SNHL has been reported infrequently in other rickettsial infections.[12] Proposed mechanisms include vasculitis affecting labyrinthine vessels, direct bacterial invasion of inner ear structures, and immune-mediated cochlear damage.[13] Bilateral moderately severe to severe SNHL documented on audiometry highlight significant morbidity. Although partial improvements were noted, complete recovery was not achieved, indicating the potential for permanent disability. Early recognition and treatment are crucial; however, the critical window for reversibility remains undefined.[14] The concurrent presentation of septic shock and multiple organ dysfunction in this patient further illustrates the severity spectrum of scrub typhus, necessitating intensive care and prompt antimicrobial therapy.

The diagnostic challenges associated with scrub typhus are multifaceted. Nonspecific clinical presentations, the absence of pathognomonic clinical signs (eschar, when present, is a valuable diagnostic clue that can significantly narrow the differential diagnosis), geographical distribution, limited access to advanced diagnostic facilities, and low clinical suspicion contribute to underdiagnosis, particularly in rural settings.[1,3] The absence of an eschar in cases 1 and 3 further exemplifies this diagnostic dilemma, necessitating a broad differential diagnosis for acute febrile illnesses with neurological involvement. When present, a characteristic maculopapular rash can aid in narrowing the differential diagnosis in the appropriate clinical context. Rapid and accurate diagnosis based on serological tests is vital . While IFA remains the gold standard with sensitivity of 85-95% and specificity of 90-98%, IgM ELISA offers a practical alternative with sensitivity of 78-88% and specificity of 82-94%, along with advantages of easier performance, lower cost, and wider availability in resource-limited settings, making it the preferred diagnostic tool in many endemic regions.

Recent literature increasingly emphasises the variability of scrub typhus presentations and the importance of considering it in unexplained febrile illnesses in endemic areas. Studies from India continue to report a high prevalence and diverse manifestations of this condition.[3,7] Advances in molecular diagnostics using blood or eschar swab specimens for polymerase chain reaction (PCR) testing, although not routinely available in all rural centres, offer more precise identification of *Orientia tsutsugamushi*.

From a public health perspective, increased awareness among clinicians is crucial. Educational programmes for healthcare providers in endemic regions should focus on the diverse clinical spectrum of scrub typhus, including atypical neurological complications. Prompt empirical

treatment with doxycycline should be considered for patients with suspected scrub typhus while awaiting confirmatory tests, especially in cases with severe neurological symptoms, as delays can lead to irreversible complications and increased mortality.

Conclusion

Scrub typhus continues to be a major public health challenge in endemic regions, such as Tamil Nadu, India. This case series underscores the profound clinical variability of its neurological manifestations, ranging from meningoencephalitis and acute myopathy to sensorineural hearing loss in the same patient. The absence of classical signs, such as eschar in many cases, necessitates a high index of clinical suspicion for scrub typhus in any patient presenting with acute febrile illness and unexplained neurological symptoms.

Early and accurate diagnosis, primarily through serological testing, followed by timely initiation of doxycycline-based therapy, is paramount for favourable outcomes and prevention of permanent sequelae. In cases with significant inflammatory or immune-mediated responses, adjunctive steroid therapy may be beneficial. Increased clinical awareness, improved diagnostic accessibility in rural settings and continuous medical education are crucial for effectively managing this re-emerging tropical disease and reducing the associated morbidity and mortality. Future research should focus on understanding the precise immunopathogenesis of atypical manifestations and optimising treatment strategies as required.

Declarations

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Author contributions:
JVT: Conceptualisation, direct patient management, data collection, analysis, initial manuscript drafting, review and editing of final manuscript.
BMB: Audiological evaluation and data interpretation of case 3, initial draft of sections on sensorineural hearing loss, review of final manuscript.

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