Case Report

DOI: 10.7860/JCDR/2021/49948.15515

Scrub Typhus with Guillain-Barré Syndrome: An Atypical Sequela due to Delayed Diagnosis

Internal Medicine Section

MAYANK AGARWAL[1], AISHWARYA[2], MUKESH BAIRWA[3], RAVIKANT[4]

ABSTRACT

Scrub typhus is a zoonotic infection which is endemic to the tropical regions of South-East Asia including the sub-Himalayan belt of North India. Clinical manifestations of scrub typhus range from self-limiting acute febrile illness to sometimes fatal multi-organ involvement. However, it does not usually involve the central nervous system, if affected meningoencephalitis is the most common presentation. Hereby the authors report a 60-year-old patient of scrub encephalitis who developed acute onset ascending, symmetric flaccid quadriparesis with sensory involvement. Electrophysiological studies and demonstration of antiganglioside antibodies confirmed the diagnosis of AMSAN variant of Guillain-Barré syndrome. The patient was treated successfully with five days of intravenous immunoglobulins. She became ambulatory with complete recovery four weeks after discharge. Guillain-Barré syndrome is a treatable entity and should be evaluated in all cases of scrub typhus having a similar presentation. It can lead to a diagnostic challenge that can often be missed as it is a rare presentation of scrub infection. Therefore, prompt diagnosis and treatment is necessary for better outcomes.

Keywords: Encephalitis, Quadriparesis, Rickettsia

CASE REPORT

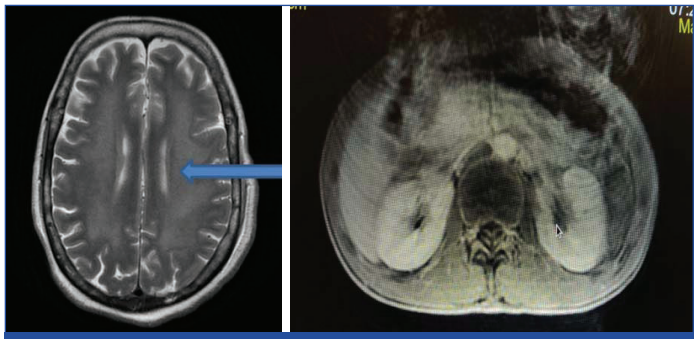
A 60-year-old female, without any co-morbidities, presented with complained of high-grade fever for five days. It was associated with chills and holocranial headache. There was no history of vomiting, dizziness, diplopia, altered mentation, cough, chest pain, abdominal pain, dysuria, or rashes over the body.

On examination, the patient was conscious and following commands. She had a pulse rate of 110 per min, blood pressure of 110/60 mm Hg, and axillary temperature of 101.2° F. There was no visible rash or eschar. Neurological examination revealed neck stiffness with a positive Kernig's sign. There was no focal neurological deficit. General and other systemic examination findings were unremarkable.

Cerebrospinal Fluid (CSF) analysis was done which showed albumin-cytological dissociation with a cell count of-10/mm^3 (normal range 0-5 cells/mm^3), with 60% neutrophils and 40% lymphocytes, protein-152 mg/dL (normal 0-45 mg/dL) and sugar was 56 mg/dL. Culture showed no growth and potassium hydroxide mount was negative for fungal elements. CSF Adenosine Deaminase (ADA) was within normal range. Keeping a possibility of acute meningitis, she was started empirically on intravenous ceftriaxone and vancomycin along with dexamethasone. The patient showed clinical improvement, however on third day of her hospital admission she again had fever spikes. She was confused and could not follow verbal commands (Glasgow Coma Scale- E2V4M4). She also developed weakness in her lower limbs which progressed to involve both her upper limbs over the next 24 hours. Neurological examination revealed flaccid tone with a power of 2/5 and 1/5 in bilateral upper and lower extremities. Deep tendon reflexes were absent and plantar reflex was mute.

A contrast enhanced Magnetic Resonance Imaging (MRI) of the brain with whole spine was done which showed hyperintensities in bilateral corona radiata, periventricular grey matter along with contrast enhancement of nerve roots in the dorsal spinal cord [Table/Fig-1,2].

She was then investigated for tropical fevers endemic in the sub-Himalayan regions of North India. *Orientia tsutsugamushi* antibody titres (by immunofluorescence assay) were elevated IgM 1:640 (normal- 1:10). Her haemogram showed a total leucocyte count of 13.4×10^9/L (neutrophils 43%, lymphocytes 56%), erythrocyte sedimentation rate was 72 mm in first hour. Other investigation including liver and renal function test, urine analysis and blood cultures were normal [Table/Fig-3].



[Table/Fig-1]: Contrast MRI brain showing T2 weighted image showing hyperintensities in corona radiata (Arrow). **[Table/Fig-2]:** Contrast Enhanced Magnetic Resonance Imaging (MRI) spinal cord-transverse section showing contrast enhancement of nerve roots (Arrow). (Images from left to right).

She was started on intravenous doxycycline along with supportive care. A Nerve Conduction Study (NCS) was done on sixth day of admission which showed markedly reduced sensory conduction in upper limb with absent conduction in bilateral peroneal and tibial nerves [Table/Fig-4]. There was reduced amplitude of compound muscle action potential and prolonged distal latency in the respective nerves along with minimal slowing of conduction velocity [Table/Fig-3]. Findings was suggestive of sensory and motor axonal pattern of polyneuropathy with lower limb predominance [Table/Fig-5,6]. A Ganglioside antibody profile was sent which was positive for anti-GM1, anti-GD1a and anti-GD1b IgG antibodies.

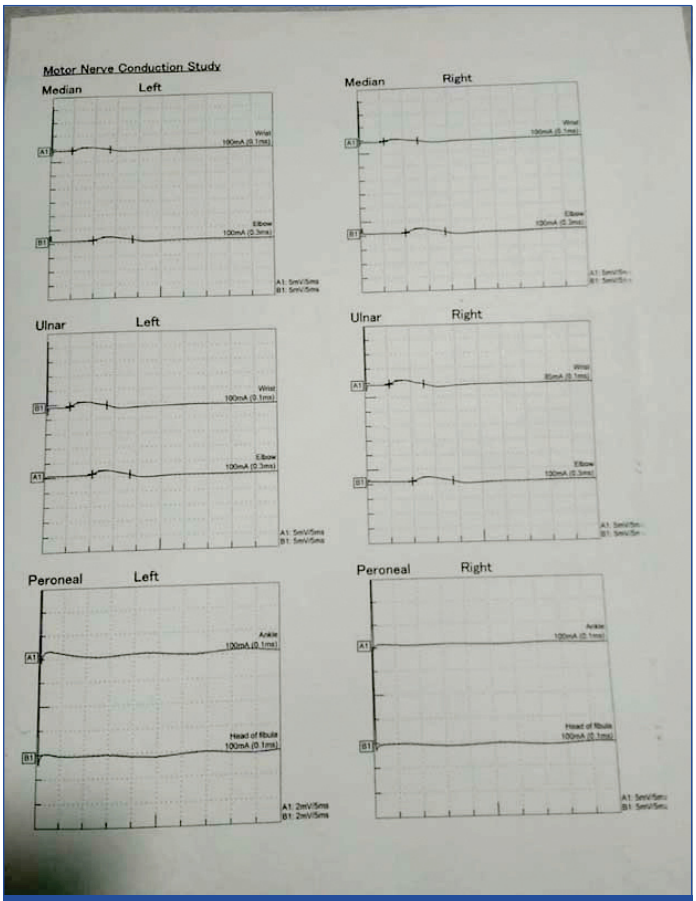
In view of the clinical presentation, CSF findings and electrophysiological studies a diagnosis of scrub meningoencephalitis complicating with Acute Motor-Sensory Axonal Neuropathy (AMSAN) variant of Guillain-Barré syndrome was kept. The patient was given Intravenous Immunoglobulin for five days (400 mg/kg/day) following which she improved significantly. She was discharged after three weeks of hospital stay with power of 4/5 in both upper and lower limbs. On follow-up, one month after discharge, she had recovered fully with no residual weakness. A repeat NCS was done which was normal.

Nerve stimulated	Segment	Response latency (ms)			Response amplitude (mV)			Conduction velocity (m/s)		
		Normal	Right	Left	Normal	Right	Left	Normal	Right	Left
Median	Wrist	<3.8	5.8	4.8	>6	1.6	1.2	>50	52	53
	Elbow		10.1	10.0		1.3	1.0			
Ulnar	Wrist	<3.0	5.4	5.3	>8	1.1	1.4	>51	49	55
	Elbow		9.9	10.4		1.4	1.1			
Peroneal	Ankle	<5.0	NR	NR	>1.5	NR	NR	>45	NR	NR
	Head of fibula		NR	NR		NR	NR			
Tibial	Ankle	<5.2	NR	NR	>6	NR	NR	>41	NR	NR
	Popliteal		NR	NR		NR	NR			

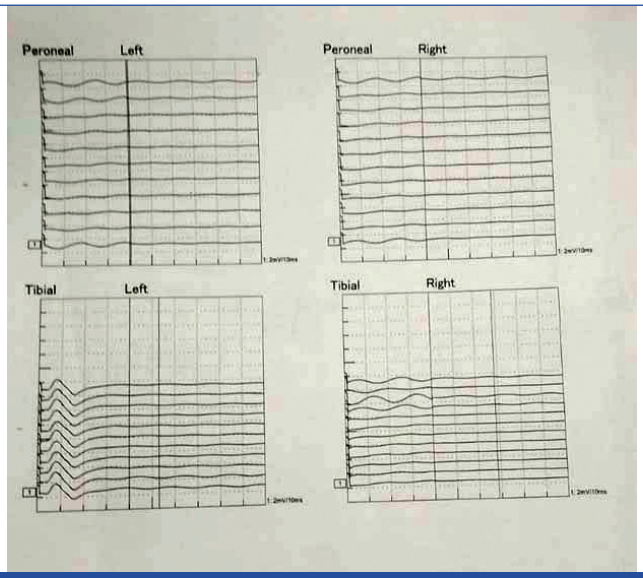
[Table/Fig-3]: Motor Nerve Conduction Study (NCS) showing reduced amplitude and prolonged distal latency (lower limb predominant).
NR: No response

Nerve stimulated	Response latency (ms)		
	Stimulus (mA)	Right	Left
Median	37	NR	NR
Ulnar	29	NR	NR
Sural	40	NR	NR

[Table/Fig-4]: Sensory Nerve Conduction Study (NCS) showing absent response in all limbs.



[Table/Fig-5]: Motor Nerve Conduction Study (NCS) showing reduced amplitude (lower limb predominant).



[Table/Fig-6]: Sensory Nerve Conduction Study (NCS) showing absent response in the tested nerves.

DISCUSSION

Scrub typhus is an acute febrile zoonosis caused by rickettsia infection. It mostly affects individuals who are exposed to the mite infested habitat in the tropical regions of South-east Asian countries [1]. Scrub can be a great masquerader with myriad of presentations. Clinical manifestations range from mild undifferentiated febrile illness that is usually self-limiting to sometimes fatal organ involvement leading to Multi-Organ Dysfunction Syndrome (MODS) [2,3]. Due to an unpredictable clinical course and often atypical presentations a high degree of clinical suspicion must be kept for its timely diagnosis and treatment to prevent complications.

Scrub typhus usually does not involve the central nervous system [4]. Meningoencephalitis is the most common neurological presentation. Other manifestations include seizures, delirium, hearing loss, cerebellitis, myelitis, infarction, haemorrhage, etc., [5]. A case study conducted in Assam medical college to determine the case load contributed by scrub encephalitis found that 20.3% of the acute encephalitis syndrome cases were attributed to scrub infection. In the same study the prevalent presentation of scrub encephalitis was fever, altered sensorium, headache, and nausea. The classically described eschar was seen in none of the cases [6]. This was similar to the index patient, where eschar was absent. She developed meningoencephalitis following scrub infection which later led to acute onset flaccid quadriparesis as a sequela.

Involvement of the peripheral nerves is an uncommon complication of scrub typhus [7]. The incidence of Guillain-Barré syndrome following scrub encephalitis has been rarely reported. In all reported cases the presentation was similar with a patient diagnosed with scrub or scrub encephalitis developing acute onset ascending flaccid paralysis associated with are flexia [4,8]. The present report probably is a first case of AMSAN variant of Guillain-Barré syndrome following scrub encephalitis, in India. Although the exact mechanism of pathogenesis is not completely understood, neuropathy may be induced by molecular mimicry, toxins, or immune dysregulation [9]. It is postulated that since *Orientia tsutsugamushi* is antigenically heterogeneous, few of the epitopes may be responsible in the cross-reactivity with gangliosides on axonal or Schwann cell membranes giving a plausible explanation for the different subtypes of Guillain-Barré syndrome [8]. Gangliosides are important glycolipids associated with cell growth and signal transduction, and more than 100 subtypes exist [10]. A positive result for the anti-ganglioside antibodies such as GD1a and GM1

IgM, as in the index patient, further supports the diagnosis of Guillain-Barré syndrome.

Both intravenous immunoglobulins (0.4 g/kg body weight daily for five days) and plasma exchange (200-250 mL plasma/kg body weight in five sessions) are equally effective treatment options for Guillain-Barré syndrome, if given during the first two weeks of disease onset [11,12]. In a case report of scrub typhus leading to Guillain-Barré syndrome plasmapheresis was the therapeutic method used with successful results [5], while in two other publications intravenous immunoglobulin was used successfully [4,8]. The index patient responded well to five days of intravenous immunoglobulin therapy. Although Guillain-Barré syndrome is a treatable entity, patients should be observed for progression of the disease, especially within the first week of onset. Most of them show recovery with about 80% of them regaining the ability to walk independently approximately 6-12 months after disease onset [13]. Approximately, one third of hospitalised patients require mechanical ventilation due to respiratory muscle weakness. Despite advances in management mortality remains as high as 20% for ventilated patients [14]. The AMSAN variant of Guillain-Barré syndrome differs clinically from motor axonal neuropathy in terms of involvement of sensory nerves, progression and outcome. It has rapid progression with most patients requiring mechanical ventilation within a few days of symptom onset. Outcome is poor, with only 20% ambulating after one year of disease onset [15]. However, this patient did not require mechanical ventilation and became ambulatory nearly six weeks later. Hence, further studies are required to understand the risk factors which predispose an individual with scrub infection to develop Guillain-Barré syndrome and to modify them to achieve favourable outcomes.

CONCLUSION(S)

Most common Central Nervous System (CNS) manifestations in scrub typhus infections are meningoencephalitis, infarction, haemorrhage, but involvement of the peripheral nerves is rare. Since most standard textbooks do not mention this unusual presentation of scrub it creates a diagnostic and therapeutic challenge. More research must go into evaluating the predisposing factors that can cause Guillain-Barré syndrome in the setting of scrub infection, we can only conjecture that as in this case a delay in diagnosis and treatment of scrub can be one of the risk factors. Other host risk factors must be evaluated to prevent underdiagnoses and help in better management of the patient.

REFERENCES

[1] Chakraborty S, Sarma N. Scrub typhus: An emerging threat. In: Indian Journal of Dermatology. Medknow Publications; 2017. Pp. 478-85.
[2] Jiang J, Richards AL. Scrub typhus: No longer restricted to the Tsutsugamushi triangle. Vol. 3, Tropical Medicine and Infectious Disease. MDPI AG; 2018.
[3] Sood AK, Chauhan L, Gupta H. CNS Manifestations in Orientia tsutsugamushi Disease (Scrub Typhus) in North India. Indian J Pediatr. 2016;83(7):634-39.
[4] Lee MS, Lee JH, Lee HS, Chang H, Kim YS, Cho KH, et al. Scrub typhus as a possible aetiology of GuillainBarré syndrome: Two cases. Ir J Med Sci. 2009;178(3):347-50.
[5] Sawale, Upreti S, Singh TS, Singh NB, Singh TB. A rare case of Guillain-Barré syndrome following scrub typhus. Neurol India. 2014;62(1):82.
[6] Khan SA, Bora T, Laskar B, Khan AM, Dutta P. Scrub typhus leading to acute encephalitis syndrome, Assam, India. Vol. 23, Emerging Infectious Diseases. Centers for Disease Control and Prevention (CDC). 2017;23:148-50.
[7] Ju IN, Lee JW, Cho SY, Ryu SJ, Kim YJ, Kim S Il, et al. Two cases of scrub typhus presenting with guillain-barré syndrome with respiratory failure. Korean J Intern Med. 2011;26(4):474.
[8] Lee SH, Jung SI, Park KH, Choi SM, Park MS, Kim BC, et al. Guillain-Barré syndrome associated with scrub typhus. Scand J Infect Dis. 2007;39(9):826-28.
[9] Hadden RDM, Karch H, Hartung HP, Zielasek J, Weissbrich B, Schubert J, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology. 2001;56(6):758-65.
[10] Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. Arch Intern Med. 1991;151(9):1753-57. Available from: https://pubmed.ncbi.nlm.nih.gov/1888241/.
[11] Hughes RAC, Swan AV, van Doorn VA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane database Syst Rev. 2012;11;(7):CD002063.
[12] Verboon C, van Doorn P, Jacobs B. Treatment dilemmas in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry. 2017;88(4):346-52.
[13] Rajabally YA, Uncini A. Outcome and its predictors in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry. 2012;83(7):711-18.
[14] Meena AK, Khadilkar SV, Murthy JMK. Treatment guidelines for Guillain-Barré Syndrome. Ann Indian Acad Neurol. 2011;14(Suppl1):S73.
[15] Griffin JW, Li CY, Ho TW, Tian M, Gao CY, Xue P, et al. Pathology of the motor-sensory axonal Guillain-Barré syndrome. Ann Neurol. 1996;39(1):17-28.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Internal Medicine, All India Institute of Medical Science, Rishikesh, Dehradun, Uttarakhand, India.
2. Junior Resident, Department of Internal Medicine, All India Institute of Medical Science, Rishikesh, Dehradun, Uttarakhand, India.
3. Assistant Professor, Department of Internal Medicine, All India Institute of Medical Science, Rishikesh, Dehradun, Uttarakhand, India.
4. Additional Professor, Department of Internal Medicine, All India Institute of Medical Science, Rishikesh, Dehradun, Uttarakhand, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mukesh Bairwa,
Assistant Professor, Department of Internal Medicine, All India Institute of Medical Science, Rishikesh, Dehradun, Uttarakhand, India.
E-mail: drmukeshbairwa1982@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 17, 2021
- Manual Googling: Sep 15, 2021
- iThenticate Software: Sep 30, 2021 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Apr 16, 2021**
Date of Peer Review: **Jul 29, 2021**
Date of Acceptance: **Sep 16, 2021**
Date of Publishing: **Oct 01, 2021**