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 ricketsial 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.[1,2] 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.[3]

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.[4]

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.[3] Scrub typhus is an important cause of acute febrile illness in India.[4] Case fatality rate may be as high as 30% if left untreated.[5] 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.[6] Infection manifests clinically as a nonspecific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhea, and breathlessness and ranges to severe multiorgan dysfunction.[4]

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–Barre syndrome, and rarely stroke. The most common reported manifestation is meningoencephalitis.[1,8,9]

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

|                          | Case 1 | Case 2 | Case 3 | 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/mm³)          | 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 (/mm³)             | 6      | 20     | 2      | 5      | 91     |
| Protein (mg/dL)          | 81     | 64     | 57     | 91     | 45     |
| Sugar (mg/dL)            | 42     | 61     | 51     | 45     |        |
|ZN stain                  | -      | -      | -      | -      | -      |
| India Ink                | -      | -      | -      | -      | -      |
| MRI/MR venogram          | MRI brain - normal | Bilateral frontotemporal-parenchymal 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 sagittal 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...

| Outcome          | Case 1       | Case 2       | Case 3       | Case 4       | Case 5       |
|------------------|--------------|--------------|--------------|--------------|--------------|
|                  | 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

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.\(^1^,\(^2^\) CNS involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis.\(^3^\) 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%).\(^3^\) 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,\(^5^\) but cerebrospinal fluid findings can mimic tuberculous meningitis and viral meningoencephalitis.\(^7^\) 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.\(^10^\) 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.\(^11^\)

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.

**References**

1. Misra UK, Kalita J, Mani VE. Neurological manifestations of scrub typhus. J Neurol Neurosurg Psychiatry 2014;0:1-6. doi: 10.1136/jnnp-2014-308722.
2. Saifudheen K, Kumar KG, Jose J, Veena V, Gafoor VA. First case of scrub typhus with meningoencephalitis from Kerala: An emerging infectious threat. Ann Indian Acad Neurol 2012;15.
3. Chunchanur SK. Scrub typhus in India—An impending threat. Ann Clin Immun Microbiol 2018;1;Article 1003.
4. Peter JV, Sudarsan T1, Prakash JA, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. World J Crit Care Med 2015;4:244-50.
5. Gurunathan PS, Ravichandran T, Stalin S, Prabu V, Anandan H. Clinical profile, Morbidity pattern and outcome of children with scrub typhus. Int J Sci Study 2016;4:247-50.
6. Vivekanandan M, Mani A, PriyaYS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. J Assoc Physicians India 2010;58:24-8.
7. Drevets DA, Leenen PJ, Greenfield RA. Invasion of central nervous system by intracellular bacteria. Clin Microbiol Rev 2004;17:323-47.
Abstract

Epilepsy is a common neurological condition with varied etiological causes, with temporal lobe epilepsy being the most common. Among the varied etiologies of temporal lobe epilepsy, mesial temporal sclerosis is an important one and it presents as intracranial epilepsy. However, we describe here a case of intracranial temporal lobe epilepsy with a rather rare etiology, calcifying pseudo neoplasm of neuraxis (CAPNON) syndrome. CAPNON is a rare benign lesion that can occur anywhere in the central nervous system. The thought process till date is to excise any intracranial space occupying lesion to relieve pressure and for a better prognosis, which is not questionable. However, we feel in case of CAPNON, wait and watch protocol can be used to a better effect with radiological and clinical follow-up. Above all, surgical excision was primarily done due to imaging confusion over CAPNON and this article comes up with few key findings to clinch the radiological diagnosis of CAPNON.

Keywords: Calcifying pseudo neoplasm of neuraxis, cavernoma, epilepsy, pseudoneoplasm

Calcified Pseudo neoplasm of the Neuraxis (CAPNON) – A Rare Cause for Temporal Lobe Epilepsy: Not all Warrant a Surgical Intervention

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Introdution

Calcifying pseudo neoplasm of the neuraxis (CAPNON) is a rare entity with only 90 cases being reported in literature till date. Among the reported 90 cases, 54 (60%) are intracranial and 36 (40%) are intraspinal lesions.

It was first identified by Miller and erroneously reported as fibro-osseous lesion in 1922. It has been synonymously termed as brain stones, fibro-osseous lesions, and calcifying pseudo tumors.

In 1978, it was reported as a distinct entity by Rhodes.[2-4] If intracranial, it can be either intra or extra-axial in location.[2,5] This entity mimics many calcifying intra-axial lesions like ganglioglioma, oligodendroglioma, cavernous malformation, and infection like tuberculosis. Hence, CAPNON should always be considered in the list of differential diagnosis for calcifying intra-axial lesions.[6]

Few patients have presented with hallucinations and partial seizures. Here, we illustrate a case presenting with intracranial temporal lobe epilepsy and eventually diagnosed as CAPNON on imaging which was conservatively managed with a good clinical outcome.

Case History

A male patient came to emergency room with five episodes of seizures since morning involving the right upper and lower limbs with secondary generalization. He was a known case of seizure disorder for the past 5 years and on anti-epileptic medication which includes eptoin and valproate. Based on clinical symptoms, the patient was referred for CT examination.

Non-contrast CT scan revealed multiple thick amorphous calcifications involving the right gangliocapsular region involving the genu and posterior limb of internal capsule, lentiform nucleus, right hippocampus, and right peduncle of midbrain [Figure 1a and b]. The patient was further evaluated with MRI with intravenous Gadolinium.