Review Article

Neuropsychiatric Manifestations of Scrub Typhus

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ABSTRACT

Scrub typhus is caused by *Orientia tsutsugamushi* characterized by focal or disseminated vasculitis and perivasculitis which may involve the lungs, heart, liver, spleen and central nervous system. It was thought to have been eradicated from India. Recently it is being reported from many areas of India. The clinical picture and severity of the symptoms varies widely. The neurological manifestations of scrub typhus are not uncommon but are diverse. Meningoencephalitis is classical manifestation of scrub typhus but cerebellitis, cranial nerve palsies, plexopathy, transverse myelitis, neuroleptic malignant syndrome and *Guillan-Barré* syndrome are other manifestations reported in literature. The availability of literature on the neurological manifestations of scrub typhus is limited to case reports mainly. This article reviews various neurological manifestations of scrub typhus reported in literature.

KEYWORDS: Himachal Pradesh, meningoencephalitis, rickettsia, rickettsial diseases

INTRODUCTION

“*Typhus*” has been derived from Greek word “*Typos*” for “fever with stupor” or smoke and refers to the cloudy sensorium of patients of severe rickettsioses. Scrub typhus is caused by *Orientia tsutsugamushi*, transmitted to humans by bite of larval stage of trombiculid mites. It is an acute febrile, infectious illness and is endemic to a part of the world known as the “tsutsugamushi triangle” which extends from Northern Japan and Far-Eastern Russia in the North, to Northern Australia in the South, and to Pakistan and Afghanistan in the West. Scrub typhus is a documented disease in many parts of India.^[1-4]

The disease is characterized by fever, headache, myalgia, cough, injected conjunctiva, and gastrointestinal symptoms. An eschar at the site of chigger bite, regional lymphadenopathy, and a maculopapular rash may provide a clue to diagnosis. The severity of the symptoms varies widely, depending on the susceptibility of the host, and the virulence of the bacterial strain. An eschar at the site of bite is seen in 50% of patients with primary infection and 30% of patients with recurrent infection. Generalized lymphadenopathy and splenomegaly may also be present; some patients may have pulmonary, central nervous system (CNS), and cardiac involvement. The disease is characterized by focal or disseminated

vasculitis and perivasculitis which may involve the lungs, heart, liver, spleen, and CNS.^[1-4] Detection of *O. tsutsugamushi* by pooled antigen ELISA has shown very good sensitivity (94%) and specificity (91%).^[5]

PATHOGENESIS

These organisms are spread to humans through the bite of the larval stage of trombiculid mites and cause a systemic disease. The neurological manifestations are similar in many respects to other rickettsial diseases in that headache is nearly always present. *O. tsutsugamushi* parasitizes endothelial cells in the periphery as well as in the brain, but it also can be found in macrophages of the liver and spleen. The mechanism of cellular invasion is not known, but binding to nonprofessional phagocytes may involve interaction between cell surface heparan sulfate proteoglycans and bacterial lectins. Infection of host cells triggers a response, including the activation of the transcription factors nuclear factor- κ B (NF- κ B) (in macrophages) and NF- κ B and AP-1 (in endothelial cells), leading to subsequent expression of chemokine genes for MIP-1 α/β , MIP-2, and MCP-1 in macrophages and MCP-1, IL-8, and RANTES in endothelial cells.

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O. tsutsugamushi was shown to induce apoptosis in an endothelial cell line. However, it inhibited the apoptotic process in monocyte-like THP-1 cells and might also actively suppress cytokine production by infected macrophages.

In vitro experiments show that *O. tsutsugamushi* infects neutrophils and macrophages as well as nonprofessional phagocytes, including fibroblasts and endothelial cells. After internalization, it escapes from phagosomes by an unknown mechanism and then proliferates in the cytoplasm. The mechanism for cell-to-cell spread is through budding of membrane-coated bacteria from infected cells.

Dissemination of bacteria from the periphery to the CNS is hematogenous. Compared with other rickettsiae, *O. tsutsugamushi* is more frequently found in circulating mononuclear cells during naturally acquired infection of humans and during experimental infection of dogs and nonhuman primates. Moreover, infection can be transmitted by blood transfusion due to prolonged microbial survival in leukocytes. These findings suggest that phagocyte-facilitated infection could play a role in CNS invasion.^[6-8]

The pathological findings in CNS in scrub typhus include diffuse or focal mononuclear cell exudates in leptomeninges and presence of typhus nodules (cluster of microglial cells) that are distributed throughout brain substance.^[9] A large study showed that CNS was involved at least slightly in almost all patients suffering from scrub typhus, however, focal neurological deficit occurred rarely.^[10]

In a series of 25 patients who underwent lumbar puncture in the absence of overt CNS signs, 48% had a reactive spinal fluid showing a mild mononuclear pleocytosis, and *O. tsutsugamushi* was identified by polymerase chain reaction (PCR) in 24% indicating that CNS invasion is much more common than is suggested by symptoms alone. Necropsy studies show brain parenchymal lesions but in contrast, the meninges are more commonly involved by *O. tsutsugamushi* than by other rickettsial infections. The overall histological picture in the CNS is best described as a meningoencephalitis.^[6-8]

CLINICAL FEATURES

Meningitis/meningoencephalitis

Meningitis/meningoencephalitis has been reported in 14%–83% of patients with scrub typhus.^[7,11,12] In a series of 37 patients with scrub typhus, 31 had altered sensorium, and 6 of them were deeply comatose. Patients presented with meningoencephalitis (35%), encephalopathy (24%), and encephalitis (16%). Nine (24%) patients had seizures,

8 (22%) patients presented with status epilepticus.^[7] In a study by Rana *et al.*, 37 patients with symptoms and/or signs suggestive of neurological dysfunction were included in the study. Of these, 31 (84%) patients had altered sensorium, 15 (40%) had meningoencephalitis, 3 (8%) had seizures.^[13]

Acute disseminated encephalomyelitis

Chen *et al.* reported a 77-year-old man admitted with fever, convulsions, and an altered level of consciousness. On neurological examination, he was stuporous with nuchal rigidity and had left hemiparesis. Serial cranial magnetic resonance images (MRI) demonstrated progressively extensive areas of signal hyperintensity on conventional T2-weighted and fluid-attenuated inversion recovery sequence images, mainly affecting the periventricular white matter. After administration of parenteral minocycline and intravenous high-dose corticosteroid, the patient had limited improvement.^[14]

Cranial nerve involvement

The involvement of 2nd, 3rd, 6th, 7th, and 8th cranial nerves has been documented in patients with scrub typhus.

Kim *et al.* reported a 69-year-old man suffering from scrub typhus, who developed ptosis and ophthalmoplegia with a focal nodular lesion in the anterior cavernous sinus detected with MRI. The ptosis and ophthalmoplegia resolved after treatment with doxycycline.^[15] A study by Rana *et al.* reported a patient with bilateral papilledema without focal deficit with normal brain imaging.^[13] Cho *et al.* reported bilateral optic neuritis with scrub typhus.^[16] Rana *et al.*, Kim *et al.*, and Lee *et al.* described 6th nerve palsy in patients suffering from scrub typhus.^[13,17,18] A 49-year-old man who had fever, malaise, headache, oliguria, and tea-colored urine. Bilateral pneumonitis, acute renal failure, acalculous cholecystitis, and aseptic meningitis were diagnosed after a series of examinations. The patient recovered after doxycycline treatment, but he developed bilateral facial palsy during the convalescent phase, which improved after the administration of a steroid. The diagnosis of infection with *O. tsutsugamushi* was confirmed.^[19] The presence of unilateral or bilateral deafness may occur in many rickettsial diseases and mechanism for hearing loss has been assumed to be vasculitis induced cochlear damage; however, it could be immune mediated also. The presence of hearing loss concurrent with fever is reported by as many as one-third of patients with scrub typhus and is a useful diagnostic clue to scrub typhus in endemic areas.^[20]

Cerebellitis

Mahajan *et al.* reported a 22-year-old female of scrub typhus with progressive swaying while walking for

3 days. She was febrile for 12 days and had jaundice and conjunctival suffusion. Neurological examination revealed scanning speech, square wave reflexes, hypotonia, impaired finger nose, knee heel tests, rebound phenomenon, and dysdiadokokinesia. Rest of neurological examination was unremarkable. MRI scan of the brain showed uniform enhancement of pachymeninges with edema of bilateral cerebellar hemisphere. She improved with doxycycline and dexamethasone. A study by Rana *et al.* reported cerebellitis in 11% cases of scrub typhus with neurological involvement. Cerebellitis occurred in isolation and in association with generalized neurological involvement also.^[13,21] Misra *et al.*, Viswanathan *et al.*, and Karanth *et al.* have reported cerebellar involvement in scrub typhus.^[7,22,23]

Cerebrovascular accident

Chung *et al.* presented a patient with a 2-week history of fever and chills, along with a 1-week history of skin rash. Scrub typhus was diagnosed with indirect immunofluorescence test and a nested PCR. Azithromycin intravenously was initiated after hospital admission. However, the patient progressed to a semi-coma on the 3rd day of hospitalization. Brain computed tomography (CT) scan showed extensive subdural hemorrhage in the left fronto-temporal-parietal area, along with subfalcine herniation. The patient became comatose and died. A 53-year-old woman presented with a 20-day history of maculopapular skin rashes on the anterior chest and a 5-day history of fever, headache, and nausea. Her headache persisted despite treatment with rifampicin. CT scan revealed a focal hyperdensity and a small amount of blood in the right cerebral hemisphere on CT scan of the brain.

They have reported another 74-year-old male hospitalized for undergoing treatment of scrub typhus and became afebrile after 3 days; on next day, he developed weakness of the left side of body. MRI of the brain indicated recent onset infarction in the right middle cerebral artery territory. They noted that the scrub typhus patients with a cerebrovascular accident (CVA) experienced a statistically significant delay in receiving effective antibiotics. Early effective antibiotic treatment may prevent the disease from progressing to disseminated intravascular coagulation in scrub typhus patients. However, the homeostatic dysfunction of endothelial cells may continue if appropriate treatment is delayed. This endothelial dysfunction and vascular events may be related. However, it was difficult to conclude that *O. tsutsugamushi* was the direct cause and it may have acted as a provoking factor for CVA.^[24] Rana *et al.* also reported one patient of scrub typhus with hyperacute hemorrhagic focus in the right temporal

lobe with microhemorrhages and another patient with prominent ventricular and extra-axial space with periventricular ooze.^[13]

Cerebral venous thrombosis

Jena *et al.* reported a 48-year-old man with fever headache and vomiting for 5 days followed by the right side focal seizures and altered sensorium for 2 days. Neurological examination revealed Glasgow Coma Scale score was (E3V3M5), bilateral papilledema, paucity of the right side movement with hypoesthesia, and an extensor plantar response on the right side. Diagnosis of scrub typhus was confirmed by serum IgM ELISA. MRI of the brain showed thrombosis of the anterior portion of superior sagittal sinus with hemorrhagic venous infarct in the left frontal lobe and a midline shift. He was treated with doxycycline and azithromycin, and emergency left front temporoparietal decompressive hemicraniectomy was done. After 6-month follow-up, he had improved and repeat brain MRI showed marked improvement with complete recanalization of the superior sagittal sinus and reduction in size of the left high frontal hematoma.^[25]

Parkinsonism

Chiou *et al.* presented a 55-year-old man who experienced acute onset bilateral limb tremor, rigidity, and myoclonus with small-stepped gait, and skin rash involving the trunk and limbs, after a fever. Serum was positive for anti-*O. tsutsugamushi* IgM antibody. MRI brain was normal. The fever improved with oral doxycycline, and the Parkinsonism and myoclonus improved with amantadine and clonazepam.^[26] Premaratna *et al.* reported a 62-year-old presented with high fever with malaise, myalgia, and arthralgia for 17 days. On the 5th day of illness, he developed intermittent resting tremor in his right arm and leg associated with stiffness, difficulty in carrying out normal work, and difficulty in smiling. He denied similar previous episodes. There were no other associated neurological manifestations. Clinical examination revealed a high amplitude low frequency resting tremor in his right hand, a mask-like face and increased muscle tone limited to the right side with normal reflexes. He had an eschar over the abdomen and immunofluorescence assay against *O. tsutsugamushi* was positive. With oral doxycycline and azithromycin, his fever settled within 48 h and a complete recovery.^[27]

Opsoclonus and myoclonus

D'sa *et al.* presented a patient of scrub typhus with gradual onset of headache for 2 days, which was associated with difficulty in seeing objects clearly; his family members also noted that his eyes were moving irregularly in different directions. His ophthalmic examination showed spontaneous rapid saccades in all directions of gaze with

normal voluntary movement in all directions, without restriction of eye movement in any direction and normal visual acuity. He had complete recovery with doxycycline therapy.^[28] Opsoclonus reflects an abnormality of the tonic inhibitory control of horizontal and vertical saccadic burst neurons exerted by “pause cells” in the parapontine reticular formation. It complicates various medical diseases, including viral infections, toxin, encephalitis, brain tumors, and paraneoplastic syndromes. Nam *et al.* and Misra *et al.* also reported opsoclonus associated with scrub typhus.^[7,29]

Misra *et al.* reported a patient of scrub typhus with stimulus-sensitive myoclonus which improved with doxycycline therapy.^[7]

Transverse myelitis and longitudinally extensive transverse myelitis

Lee *et al.* reported a case of acute transverse myelitis temporally associated with scrub typhus. It is a result of autoimmune response to myelin basic protein triggered by infection or immunization. Diagnosis is usually made in the setting of recent infectious illness on the basis of clinical findings with aid of MRI and cerebrospinal fluid (CSF) examination. CSF findings include mononuclear pleocytosis and elevated protein levels. Typical MRI findings are areas of increased signal intensity in spinal cord on T₂-weighed images.^[30]

A 35-year-old female presented with fever, headache for 4 days followed by weakness of both lower limbs with diminution of pain and retention of urine. There was an eschar on anterior abdominal wall. On examination, power and tone were decreased in lower limbs, all deep tendon reflexes, and superficial abdominal reflex were absent. Plantar reflexes were mute. Her touch, pain, and temperature sensations with position and vibration sensation were markedly decreased below umbilicus along. MRI spine revealed altered signal intensity involving spinal cord in region of C4-D11 suggestive of longitudinally extensive transverse myelitis. She was treated with doxycycline and methylprednisone. She improved and was able to walk with support.^[31]

Guillain-Barré syndrome

A 60-year-old male visited the emergency department after suffering weakness of the lower extremities for 2 days. Ten days before the visit, he had visited a local private clinic for headache and chills. After being diagnosed with scrub typhus, he was treated with doxycycline. His symptoms marginally improved, but weakness in both lower extremities developed. Two days after admission, weakness in both extremities progressed (upper, Grade II; lower, Grade II), and he developed a mild disturbance of consciousness. Serum

antiganglioside antibodies, GD1b IgG and GM1 IgG, and anti-myelin-associated glycoprotein antibody were negative, but GM1 IgM and GD1b IgM antibodies were positive. An electromyography showed diffuse demyelinated neuropathy, which was prominent in the lower extremities. Intravenous immunoglobulins were administered for 5 days (22 g, 400 mg/kg/day), and doxycycline was maintained at 100 mg/12 h (PO). On day 4 after admission, the patient complained of dysphagia and dyspnea. The patient required mechanical ventilation due to respiratory muscle weakness. Eleven days after admission, he recovered spontaneous breathing, and the ventilator was removed. At 48 days after admission, his manual muscle testing grade recovered to normal, and he was discharged without complications.^[32]

Lee *et al.* described Guillain-Barré syndrome (GBS) associated with scrub typhus. The diagnosis of GBS was based on neurological examination and electromyography. *O. tsutsugamushi* antibody or antigens presented on infected cells are suspected to activate mimicry on myelin cells or peripheral nerve axons, which elicits immune reactions similar to autoimmune diseases. A positive result for the antiganglioside antibodies GD1b and GM1 IgM supports the conclusion that mimicry between pathogenic antigens and the myelin of peripheral nerves caused the immune reaction and GBS.^[33] Miller Fisher syndrome following scrub typhus infection has also been reported.^[34]

Plexopathy and peripheral neuropathy

Ting *et al.* reported a 20-year-old man who had scrub typhus with the unusual neurologic complication of brachial plexus neuropathy. Brachial plexus neuropathy was proven by an electrophysiologic examination. He had a nearly complete recovery after adequate medical treatment.^[35]

Kim *et al.* described a 64-year-old man with scrub typhus who presented with both polyneuropathy and cerebral infarction. The neurological examination revealed a confused mental state, stiff neck, hearing impairment, symmetric weakness, sensory loss, and ataxia. Electrophysiologic studies showed demyelinating sensorimotor polyneuropathy and sensorineural hearing loss. Brain MRI imaging showed multiple infarctions.^[36]

Neuroleptic malignant syndrome-like presentation

A 36-year-old patient with scrub typhus presented with fever, altered sensorium with marked rigidity all over the body and was not on neuroleptic agents. Creatine phosphokinase was markedly raised (1849 IU/L), and MRI Brain was normal. The clinical presentation was similar to neuroleptic malignant syndrome; however,

CSF protein-27 mg%, sugar-58 mg%, and cell-78 PHF mostly lymphocytes.^[13]

Psychiatric manifestations

Mahajan *et al.* reported a 63-year-old woman presented with fever, diffuse headache, and body aches for the previous 10 days. She had eschar and IgM antibodies for *O. tsutsugamushi* were also positive by ELISA. She was improving on doxycycline, and on 6th day of admission, she suffered two episodes of visual hallucinations of acute onset, perceiving animals and dead relatives; she was alert but confused. There was no other neurological deficit noted. Her laboratory tests had normalized. A CSF examination during one such episode was likewise normal. The hallucinatory symptoms lasted for 12 h and subsequently improved.^[37]

The alteration in consciousness of a patient of scrub typhus can be attributed to multiple factors. The classic changes in consciousness of a patient of scrub typhus have been described as delirium similar to other rickettsial and bacterial febrile illnesses.^[1-3,6,7] In delirium, abnormal behavior is associated with changes in consciousness levels also. It is different from other psychotic conditions where abnormal behavior is seen with impaired insight without alterations in consciousness. The presence of psychiatric disturbances toward the end of 1st week of illness is known to occur in another rickettsial illness (epidemic typhus) also.^[1] However, occurrence of neuropsychiatric manifestations in scrub typhus is not a commonly reported entity in literature. Ripley^[38] has described the presence of neuropsychiatric disorders in scrub typhus; similarly, Wisseman^[39] has also described the association of neuropsychiatric abnormalities with scrub typhus.

INVESTIGATIONS

Cerebrospinal fluid examination

The CSF studies of patients with scrub typhus had revealed mild-to-moderate pleocytosis (mainly mononuclear) in 48% of the patients, normal glucose levels, and a mild increase in the protein levels in 30% of patients. These findings are similar to those of viral meningitis. There was presence of erythrocytes in the CSF of some cases this can be attributed to the presence of generalized vasculitis.^[40]

The CSF examination in patients with scrub typhus with neurological involvement can mimic subacute meningitis-like tuberculous meningitis and viral meningoencephalitis. A study conducted by Viswanathan *et al.* had showed decreased CSF sugar level in 23% of scrub typhus patients presenting as meningitis.^[23] However, CSF sugar can be normal.^[22,40,41] Pai *et al.* have demonstrated the presence of rickettsiae in CSF

samples from patients with scrub typhus using nested PCR.^[41]

Neuroimaging

In a series of 37 patients with scrub typhus with neurological involvement, 31 patients had altered sensorium. MRI was performed in 25 patients and was normal in 24; only one patient showed meningeal enhancement.^[7] Viswanathan *et al.* has also reported normal imaging in majority of patients with scrub typhus with neurological manifestation.^[22] Sood *et al.* reported that newer and advanced MRI sequences such as susceptibility-weighted imaging and contrast-enhanced MP RAGE sequence, which is a 3-dimensional T1-weighted gradient sequence that provides excellent gray and white matter differentiation, and pick up the abnormality in the brain when these were not seen in routine MRI sequences. More research work is required to prove that new MRI sequences such as arterial spin labeling, diffusion tensor imaging, magnetic resonance spectroscopy time of flight, and dynamic susceptibility-weighted perfusion play a major role in diagnosing this rare and life-threatening, yet a treatable disease which has high mortality and morbidity rates.^[42]

Electroencephalogram

Misra *et al.* noted nonspecific generalized slowing in theta-to-delta range on electroencephalogram. No focal slowing, asymmetry, or epileptiform activity was noted.^[7]

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Conflicts of interest

There are no conflicts of interest.

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