Scrub typhus is one of the most frequent causes of acute febrile illness in South and South-east Asian countries. Neurological features accompany 20% of scrub typhus infections, and may affect the central or peripheral nervous system, and sometime, may even occur in combination. Of late, its recognition among clinicians has increased with widening detection of its cutaneous hallmark, called eschar. Multiple mechanisms underlie neurological involvement, including direct invasion (meningitis, encephalitis), vasculitis (myositis) or immune-mediated mechanisms (opsoclonus, myoclonus, optic neuritis, Guillain–Barre syndrome). Despite an immunological basis for several neurological manifestations, response to doxycycline is remarkable, although immune therapy may be necessary for severe involvement. Scientific literature on scrub typhus neurology chiefly emanates from case reports, case series and small studies, and a comprehensive review is warranted to aid clinicians in recognising neurological involvement. This review aims at enriching this gap, and summarises clinical features, laboratory findings, and treatment options for various neurological facets of scrub typhus.

Keywords: Neurology, opsoclonus, orientia tsutsugamushi, scrub typhus, vasculitis

INTRODUCTION

Scrub typhus is a rickettsial illness caused by Orientia tsutsugamushi. It is due to the bite of the larval form of the Leptotrombidium mite, termed ‘chigger’ which is both reservoir and disease vector. The larval form survives by feeding on rats, which are reservoir hosts. Humans are infected when they come in contact with chiggers. Most descriptions of scrub typhus have emanated from a distinct geographical region, termed ‘tsutsugamushi triangle.’ This triangles extend from northern Japan and eastern Russia in the north, Pakistan and Afghanistan in the west and northern Australia in the south. However, reports have also emerged from other regions such as South America and Africa, lately. Above one billion individuals are at risk for scrub typhus in endemic areas. Scrub typhus typically leads to an acute febrile illness, associated with thrombocytopenia, transaminitis and a sine qua non-cutaneous lesion at the site of the chigger bite, termed ‘eschar.’ This has a ‘cigarette burn’ appearance with an ulcer with a scab at the centre, and surrounding erythema or desquamation. The eschar occurs at specific sites of predilection, including axilla, submammary folds, gluteal cleft, inner thighs, abdomen, and lower back [Figure 1]. Orientia tsutsugamushi is an obligatory intracellular bacterium and replicates within endothelial cells and phagocytes. Hence, it has a predilection for affecting highly vascularised organs such as brain, lungs, and liver. Severity of infection is determined by immune status of the host, and the strain of O. tsutsugamushi, with Karp serotype being most prevalent in endemic regions.

Nervous system involvement occurs in up to one-fifth of the patients and is often prominent. It may affect the central or peripheral nervous system. A diverse range of neurological features have been described, ranging from the more frequent meningitis and encephalitis, to rarer phenomenon such as opsoclonus, myoclonus, parkinsonism and Guillain–Barre syndrome (GBS). The pathogenesis underlying neurological manifestations may be a combination of vasculitis or other immune phenomena triggered by the infection. Despite the potentially serious consequences, scrub typhus remains eminently amenable to therapy in the form of doxycycline. The presentations are myriad and can easily be mistaken for other tropical neurological syndromes. Although there are individual case series and reports on the neurological presentations in scrub typhus, an updated review is lacking.

In this article, we aim to evaluate the clinical and epidemiological profile, treatment outcomes and potential pathogenetic mechanisms underlying neurological manifestations of scrub typhus.

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Methods

Search strategy
We searched three major electronic databases in an attempt to locate all reports of neurological manifestations of scrub typhus published until May 2021 in the electronic form: MEDLINE (PubMed), Google Scholar and ScienceDirect were searched. Search terms were “neurology,” “encephalitis,” “meningitis,” “meningoencephalitis,” “seizure,” “parkinsonism,” “opsoclonus,” “myoclonus,” “ophthalmoplegia,” “ocular flutter,” “ataxia,” “neuropathy,” “Guillain–Barre syndrome,” “myelopathy,” “myelitis,” “cranial neuropathy,” “facial palsy,” “central nervous system.” These terms were combined with “scrub typhus” and “Orientia tsutsugamushi.”

We included original articles, case series, case reports, letters to the editor, posters and bulletins published up to May 2021 in this review, which described neurological manifestations associated with scrub typhus infection among adults (>18 years). We restricted our search to articles in English. The two authors (DG, AM) independently screened titles and abstracts of all papers located in the initial search. From these articles, we extracted author name, year of publication, journal name, age and sex of the patients, type of neurological manifestation, day of illness on which neurological feature appeared, diagnostic method, neuroimaging and other evaluation details, treatment details and outcome.

Results

Neurological features in scrub typhus can be classified as those involving the central nervous system (CNS), peripheral nervous system (PNS) and those with multi-axial involvement. Clinical, laboratory features and treatment modalities adopted have been described below.

Pathogenesis of neurological features
Approximately 20%–25% of patients with scrub typhus suffer from neurological complications, making this an important part of the clinical constellation.[5-8] Entry in to the CNS is via invasion of endothelial cells by O. tsutsugamushi. Endothelial cells are the primary cellular target. Subsequent endothelial cell activation leads to leukocyte adhesion and transmigration, platelet aggregation and cytokine release. In the lung, this uncontrolled activation causes excessive neutrophilic and monocytic infiltration, triggering acute respiratory distress syndrome (ARDS).[6] In the CNS, resultant vasculitis leads to a plethora of complications. Direct invasion of the CSF has been reported in some studies, leading to meningitis and meningo-encephalitis.[7] A third mechanism underlying neurological features is immune-mediated, due to type 2 hypersensitivity reaction targeting self-antigens. This explains certain late-onset manifestations such as opsinclonus, myoclonus, GBS and myelitis.

We have summarised these mechanisms in Figure 2 and the timeline of development in Figure 3.

Central nervous system involvement in scrub typhus
The most frequently occurring CNS manifestations include meningitis, meningo-encephalitis, encephalitis, encephalopathy and seizures. Less commonly, stroke, cerebellar involvement, opsonolus, myoclonus, cranial neuropathies, parkinsonism, acute disseminated encephalomyelitis (ADEM), haemorrhagic encephalitis and myelitis have been reported [Table 1]. The word ‘typhus’ itself is derived from ‘typhos’ indicating stupor, inspired from the diverse range of CNS involvement. CNS involvement in scrub typhus is also a predictor of mortality.[8]

In the largest prospective series, 79/189 (41.8%) patients diagnosed with scrub typhus had any form of CNS manifestations; 42 (22.2%) had altered sensorium, 12 (6.3%) had seizures, 39 patients were diagnosed to have aseptic meningitis based on CSF findings.[9]

Meningitis, encephalitis and encephalopathy
Meningitis and meningoencephalitis are the most frequent neurological features of scrub typhus, with data emanating from larger case series [Table 1]. Scrub typhus accounted for 18% of all CNS bacterial infections in Laos.[10] In a large series of patients from India, 37/323 (11.5%) patients...
with scrub typhus had CNS involvement.\[11\] In studies from India, 20%–25% cases with acute encephalitis had IgM/PCR positivity for scrub typhus although this effect is uncertain as IgM response in scrub typhus may persist for more than a year.\[12,13\]

Patients with scrub typhus meningitis present with classical clinical features of meningeal involvement.\[14\] They report fever, headache, vomiting, neck stiffness and altered sensorium. Neck stiffness may be reported in up to 67% of patients.\[5\] Presence of altered sensorium/seizures including status epilepticus and focal deficits is seen in encephalitis.\[15\] The median duration from onset of fever may ranges from 3 to 22 days as per literature. In one rare case report, haemorrhagic conversion of encephalitis was reported and was postulated to be consequent to vessel wall fragility in vasculitic blood vessels.\[16\]

Scrub typhus yields a cerebrospinal fluid (CSF) picture akin to aseptic meningitis, with lymphocytic pleocytosis, mild to moderate protein elevation and normal or borderline low sugar levels. In endemic regions, bacterial and tubercular meningitis form close differentials. Some of the pointers towards scrub typhus as the underlying aetiology of meningitis compared to tuberculosis include a relatively shorter duration of illness, less severe neurological deficits at presentation, presence of hepatic involvement, thrombocytopenia and CSF parameters including lower degree of protein elevation and lymphocytosis.\[17,18\] In comparison to acute bacterial meningitis, shorter duration of symptoms, higher levels of obtundation, absence of hepatic involvement, higher CSF pleocytosis, neutrophilic predominance in CSF and higher degree of protein elevation favour bacterial meningitis over scrub typhus meningitis.\[4\]

Although doxycycline is the treatment of choice for scrub typhus, several authors have noted the development of meningitis or meningoencephalitis during the course of doxycycline therapy. This may be due to the bacteriostatic action of doxycycline, relatively poor penetration through the blood–brain barrier and drug resistance. For this reason, some authors advocate the use of rifampicin alone or in addition to doxycycline for CNS involvement in scrub typhus. Minocycline has also been found to be effective in treatment of CNS scrub typhus with good response.\[19\] Overall, response to antimicrobial therapy is favourable with most patients responding well. However, since CNS involvement may also be mediated by immunological mechanisms apart from just direct invasion, this issue may not be related to doxycycline penetration alone.

**Cranial nerve palsies**

Individual as well as multiple simultaneous nerve involvement has been reported with scrub typhus [Table 1]. Involvement may be indirect, as a result of an immune-mediated process, such as optic nerve involvement in post-infectious optic neuritis, which is steroid-responsive. Multiple extraocular nerve involvement may occur as part of cavernous sinus inflammation or infection. The latter seem to respond well to antibiotic therapy alone. In a series of patients with meningitis due to scrub typhus, cranial nerve palsies were observed to respond to doxycycline therapy.\[15\] However, development after scrub typhus infection has been treated may raise concerns of post-infectious demyelination. Additional clues may be derived from CSF analysis, with albumin-cytological dissociation favouring inflammation over infection. Similarly, in patients with scrub typhus with lateral rectus palsy, only one patient presented with diplopia in concert with fever.\[20\] In the other two cases, it was detected on examination. Moreover, CSF was normal in two cases and showed mild elevation in protein in one patient, suggesting that the mechanism of involvement may be leptomeningeal inflammation or raised intracranial pressure or even microvasculitis-mediated nerve injury.

Hearing loss is a unique and interesting phenomenon noted in scrub typhus and is acute and reversible. It is believed to be present in nearly one-third of patients although only limited cases have been reported [Table 1].\[21\] The mechanism could be due to immune-mediated or vasculitis-related damage to the VIIIth nerve or demyelinating neuropathy involving the cochleovestibular nerve. In a histopathology study of louse-borne typhus, cochlear and retro-cochlear injury was noted.\[22\]
Table 1: Summary of studies describing central nervous system (CNS) involvement in association with scrub typhus

| Author/Year | Country   | Type of study          | No. of participants/case clinical details | Age (yrs) | Sex | Interval (days) between onset of fever and neurological symptom |
|-------------|-----------|------------------------|------------------------------------------|-----------|-----|---------------------------------------------------------------|
| Lee et al.[15]/2017 | Korea     | Retrospective case series | 16 Fever, chills, headache, vomiting in a renal transplant recipient | 35.5  | 62.5% F | 3-22 |
| Dhanapriya et al.[39]/2017 | India     | Case report             | 45                                                                      | F        | 6               |
| Sharma et al.[40]/2015 | India     | Prospective case series | 23  Range: 19-68 years | 62.5% F | Not mentioned |
| Jamil et al.[41]/2015 | India     | Prospective case series | 13 Mean 34.8±16.2   | M: F=2.25:1 | Mean 5.6±3.08 days |
| Abhilash et al.[42]/2015 | India     | Retrospective case series | 189 41±16.3                                                                       | 56.8  | Not mentioned |
| Misra et al.[43]/2015 | India     | Cross-sectional         | 37 3-71                                                                      | F        | 49             |
| Boorugu et al.[44]/2014 | India     | Prospective case series | 6  Not reported | 2-4 (mean 3) |
| Kar et al.[45]/2013 | India     | Case-control study      | 22 70                                                                      | 63.6% F | Not reported |
| Ghim et al.[46]/2006 | Taiwan    | Case report             | 77 Fever, altered sensorium, dysarthria and left hemiparesis, seizure, left facial paresis | F        | 10             |
| Chen et al.[47]/2000 | Korea     | Case report             | 77 Fever, altered sensorium, dysarthria and left hemiparesis, seizure, left facial paresis | M        | 5               |
| Kim et al.[48]/2013 | Korea     | Case report             | 22  17/65 had meningitis | 41.8±17.7 | 33 M/32 F |
| Viswanathan et al.[49]/2013 | India | Retrospective case series | 189 Fever with chills followed by headache, vomiting, stupor | 19  | F | Not reported |
| Gaba et al.[50]/2020 | India     | Case report             | 44/253 (17.4%) | 69.6% F | Not mentioned |
| Mahajan et al.[51]/2016 | India     | Retrospective           | 41.4±31.7 44/253 (17.4%) | 69.6% F | Not mentioned |
| Status epilepticus |           |                        |                                           |           |                  |
| Kalita et al.[52]/2021 | India     | Case report             | Fever, persistent altered sensorium | 50  | F | Simultaneous |
| Kalita et al.[53]/2016 | India     | Prospective             | 13/66 patients with scrub typhus had status epilepticus. 10 included. | 34 (range 18-71) | 7 females; 3 males | 4 and 30 (median 11) |
| Rapidly progressive dementia |       |                        |                                           |           |                  |
| Park et al.[54]/2017 | Korea     | Case report             | Acute cognitive impairment with reversible splenial lesions | 78  | F | Not specified |
| Posterior Reversible Encephalopathy Syndrome |       |                        |                                           |           |                  |
| Naveen et al.[55]/2020 | India     | Case report             | Fever followed by headache, hypotension, seizure and obtundation | 40  | F | 4 |
| Cranial neuropathy |            |                        |                                           |           |                  |
| Optic neuritis |          |                        |                                           |           |                  |
| Jessani et al.[56]/2016 | India     | Case report             | Fever, headache, right eye pain and visual loss | 8  | F | Not reported |
| Cho et al.[57]/2013 | Korea     | Case report             | Bilateral loss of vision two weeks after resolution of febrile illness | 8  | M | 21 |
| Bae et al.[58]/2018 | Korea     | Case report             | Post-infectious ON with NMO+ | 82  | F | 21 |

Contd...
### Table 1: Contd...

| Author/Year | Country       | Type of study      | No. of participants/case clinical details                                      | Age (yrs) | Sex | Interval (days) between onset of fever and neurological symptom |
|-------------|---------------|--------------------|--------------------------------------------------------------------------------|-----------|-----|---------------------------------------------------------------|
| Ophthalmoplegia                                   |                |                    |                                                                                |           |     |                                                               |
| Kim et al.[50]/2015                               | Korea         | Case report        | Fever followed by ptosis and ophthalmoplegia                                   | 69        | M   | 5                                                             |
| Trigeminal neuralgia                              |                |                    |                                                                                |           |     |                                                               |
| Ani et al.[51]/2007                               | Japan         | Case report        | Fever and headache followed by electric shock-like pain in the left eye        | 64        | M   | 1                                                             |
| Abducens palsy                                    |                |                    |                                                                                |           |     |                                                               |
| Ozair et al.[20]/2020                             | India         | Case report        | Fever, altered sensorium followed by diplopia                                  | 27        | F   | 6                                                             |
| Ete et al.[52]/2016                               | India         | Case report        | Fever, altered sensorium                                                       | 22        | F   | 5                                                             |
| Bhardwaj et al.[53]/2013                          | India         | Case report        | Fever, headache, altered sensorium                                              | 23        | F   | 7                                                             |
| Facial palsy                                      |                |                    |                                                                                |           |     |                                                               |
| Lin et al.[54]/2013                               | Taiwan        | Case report        | Fever and bilateral sequential facial palsy                                    | 49        | M   | 13, 23 (left, followed by right)                              |
| Hearing loss                                       |                |                    |                                                                                |           |     |                                                               |
| Premaratna et al.[55]/2005                        | Sri Lanka     | Case series        | 6 patients                                                                     |           |     |                                                               |
| Kang et al.[56]/2009                              | Korea         | Case series        | 4 (Patients 2,3 had otalgia without hearing loss)                               | 1.60      | F   | 14                                                            |
| Venketesan et al.[57]/2019                        | India         | Case report        | Loin pain, dysuria, fever, hearing loss in a diabetic                          | 52        | F   | 10                                                            |
| Oto-ocular symptoms                               |                |                    |                                                                                |           |     |                                                               |
| Nam et al.[58]/2010                               | India         | Case reports       | 2                                                                               | 64        | F   | Not mentioned                                                |
| D’sa et al.[59]/2012                              | India         | Case report        | Fever, headache, oscillopsia                                                   | 54        | M   | 5                                                             |
| Koti et al.[60]/2015                              | India         | Case report        | Fever, dyspnea, restlessness followed by opsoclonus myoclonus                  | 26        | M   | 6                                                             |
| Sahu et al.[61]/2017                              | India         | Case report        | Fever, ataxia, tremulousness, pan-cerebellar syndrome, opsoclonus               | 60        | M   | 3                                                             |
| Choi et al.[62]/2017                              | Korea         | Case report        | Fever, rash, tremors, parkinsonism                                             | 59        | M   | 8                                                             |
| Ralph et al.[63]/2019                             | India         | Case series        | 18 patients in a retrospective series had opsoclonus, of which 9 (50%) had     | -         | M   | Mean 11 days (range 7-18 days)                                |
| Saini et al.[64]/2020                             | India         | Retrospective case series | had scrub typhus in this series of children with ‘infection-associated opsoclonus’ | 7         | F   | 5                                                             |
| Garg and Dhamija[65]/2021                         | India         | Case report        | Abnormal eye and limb movement, fever                                         | 23        | F   | 7                                                             |
| Cerebellar dysfunction                            |                |                    |                                                                                |           |     |                                                               |
| Gupta et al.[66]/2020                             | India         | Case report        | Fever for 4 days followed by pan-cerebellar symptoms                           | 26        | F   | 5                                                             |

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Table 1: Contd...

| Author/Year          | Country     | Type of study     | No. of participants/case clinical details                                                                 | Age (yrs) | Sex | Interval (days) between onset of fever and neurological symptom |
|----------------------|-------------|-------------------|----------------------------------------------------------------------------------------------------------|-----------|-----|---------------------------------------------------------------|
| Kaiser et al. [64]/2020 | India       | Case report       | Fever, difficulty in walking, visual impairment                                                          | 7         | F   | 12                                                            |
| Bhat et al. [65]/2015  | India       | Case report       | Fever followed by dysarthria and cerebellar signs                                                      | 6         | F   | 3                                                             |
| Bhoil et al. [26]/2016 | India       | Case report       | Fever, semiconscious state, pan cerebellar involvement                                                  | 21        | M   | 3                                                             |
| Ddid et al. [66]/2017  | India       | Case report       | Fever, headache, vomiting, swaying to the left                                                          | 9         | M   | Not mentioned                                                |
| Karanth et al. [27]/2013 | India       | Case report       | Fever, drowsiness, cerebellar features                                                                 | 24        | M   | 12                                                            |
| Mahajan et al. [28]/2016 | India       | Case report       | Fever, headache, vomiting followed by ataxia                                                            | 22        | F   | 9                                                             |
|                          |             | Parkinsonism      |                                                                                                         |           |     |                                                               |
| Soundararajan et al. [29]/2020 | India | Case report | Fever, cough, dyspnoea, slurred speech, ret tremor, hypomimia, hypophonia                               | 50        | M   | 14                                                            |
| Ralph et al. [30]/2019  | India       | Case series reporting on opsoclonus in scrub typhus                                                      | 6/18 (33%) had EPS                                        |           |     | -                                                             |
| Premanada et al. [31]/2015 | Sri Lanka | Case report       | Fever, right sided rest tremors, stiffness right leg                                                     | 62        | M   | 5                                                             |
| Chiu et al. [32]/2013   | Taiwan      | Case report       | Fever, rash, rigidity, myoclonus, tremors                                                              | 55        | M   | 2                                                             |
| Transverse myelitis     |             |                   |                                                                                                         |           |     |                                                               |
| Ryu et al. [33]/2020    | Korea       | Case report       | Fever, headache; responded to doxycycline; then developed sudden paraparesis with bowel and bladder involvement | 66        | M   | 7                                                             |
| Yun et al. [34]/2017    | Korea       | Case report       | Fever, chills followed by ascending paraparesis (power grade 2/5)                                       | 67        | M   | 14                                                            |
| Mahajan et al. [35]/2016 | Korea       | Case report       | Fever, chills, headache, paraparesis                                                                   | 35        | F   | 4                                                             |
| Lee et al. [36]/2008    | Korea       | Case report       | Fever, headache followed by right lower limb weakness, left lower limb paresthesias, bladder involvement | 54        | M   | 7                                                             |

| Author/Year          | Diagnostic testing        | Neuro-imaging/other investigations | Treatment                              | Outcome             |
|----------------------|---------------------------|------------------------------------|----------------------------------------|---------------------|
| Lee et al. [37]/2017  | Indirect IFA              |                                    | Doxycycline with/without clarithromycin| 15/16=improved completely 1/16=persistent facial palsy |
| Dhanapriya et al. [38]/2017 | IgM ELISA           | CT normal; CSF 607 cells; protein 203 mg/dL; sugar 77 mg/dL | Oral doxycycline for 5 days followed by IV azithromycin | Responded well to azithromycin |
| Sharma et al. [39]/2015 | Weil-Felix test/Positive IgM ELISA | Median CSF cell count, CSF protein, CSF glucose/blood glucose were 17 cells/µL, 86 mg/dL, 0.6605 | Doxycycline        | No mortality        |
| Jamil et al. [40]/2015  | CT/MRI normal; Mean CSF cells 152 + 67 cells/mm³, 55 + 12.7 mg/dL, | Mean CSF protein, glucose 152.16±16.88 mg/dl, respectively. Mean total count of CSF leukocytes 46.07±131 cell/mm³; 98.66±3.09% L | Tablet doxycycline with or without injection azithromycin | 2/13 (15%) died; both has multi organ dysfunction |
| Author/Year | Diagnostic testing | Neuro-imaging/other investigations | Treatment | Outcome |
|------------|---------------------|------------------------------------|-----------|---------|
| Abhilash et al. (42)/2015 | ELISA/PCR + eschar | Mean CSF WBC count 80±120 cells/mm³ (range 5-900); mean CSF protein 105.9±80.9 (range 13-640 mg%), mean CSF sugar level 69.4±89.6 mg% (range 25-350 mg%) | Doxycycline with or without intravenous azithromycin for 7 days | 11 patients died (5.8%); Mean duration of hospital stay was 6.9 days (SD 5.1 days) |
| Misra et al. (3)/2015 | Solid phase immunochromatographic assay or Weil-Felix test | MRI revealed meningeal enhancement in only 1/25 (4%) patient and EEG showed generalised slowing in 6/28 (21.4%) | Doxycycline | Patients with low GCS score had significantly more focal neurological deficit (r=-0.5; P=0.002), longer hospital stay (r=-0.4; P=0.03) and more disability on discharge (r=-0.4; P=0.01) |
| Boorugu et al. (9)/2014 | IgM serology and/or presence of eschar | Headache- 79 (41.8%); Altered sensorium- 42 (22.2%); Seizures- 12 (6.3%); CSF (47 patients): 39 had aseptic meningitis MRI: cerebral edema, hyperintense putamen and thalamus on T2/FLAIR | Not mentioned | Not mentioned |
| Kar et al. (43)/2014 | IgM ELISA | CSF suggestive of meningitis in 2; All had renal dysfunction MRI: cerebral edema, hyperintense putamen and thalamus on T2/FLAIR | Oral doxycycline | All responded well |
| Viswanathan et al. (44)/2013 | IgM ELISA, Weil-Felix test, eschar | Median CSF cells=54, protein 88, sugar 0.622 U/mL | Doxycycline, chloramphenicol | Recovery in all patients |
| Kim et al. (40)/2013 | Positive PCR or indirect IFA | CSF TLC= median 24 cells/mm³, protein median 78 mg/dL, glucose median 56.5 mg/dL | Doxycycline, rifampicin, telithromycin | Recovery in all patients |
| Khan et al. (32)/2017 | IgM ELISA | - | - | 53/104 patients could be followed up; 26 died after discharge |
| Gaba et al. (90)/2020 | IgM ELISA | CSF cell count 16 cells µ/L; 80% lymphocytes; total protein 51 g/dL; glucose 73 mg/dL MRI: Hemorrhagic encephalitis | Ceftriaxone, doxycycline, dexamethasone, mannitol | Complete recovery |
| Mahajan et al. (29)/2016 | IgM ELISA | 18/44 had abnormal CSF | Doxycycline/azithromycin | Altered sensorium risk factor for mortality |
| Chen et al. (39)/2006 | Increase in IgG antibodies on serial serum and CSF testing during acute and convalescent phase | Serial MRIs: progressive areas of signal hyperintensity involving periventricular white matter CSF=230 cells/mm³, glucose 41 mg/dL, protein 219 mg/dL | No response to minocycline; Intravenous high dose corticosteroids | Developed coma and quadriplegia despite steroids. Limited improvement; persistent quadriplegia, transferred to a long-term care facility |
| Kim et al. (31)/2000 | Serum (IFA) and CSF IgM and IgG antibodies positive | MRI: T2/FLAIR hyperintense lesions in lower brainstem, cerebellar peduncles, spinal cord (grey matter) | Doxycycline | Complete motor recovery by day 24 |

**Status epileptics**

| Author/Year | Diagnostic testing | Neuro-imaging/other investigations | Treatment | Outcome |
|------------|---------------------|------------------------------------|-----------|---------|
| Kalita et al. (33)/2021 | IgM ELISA | MRI brain normal; EEG <=2.5 hertz generalised epileptiform discharges; CSF abnormal | Lorazepam, valproate, levetiracetam | Complete recovery |
| Kalita et al. (32)/2016 | Solid phase immunochromatography assay | MRI normal EEG normal | As for SE; all patients received doxycycline | Complete recovery at 1 month |

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Table 1: Contd...

| Author/Year | Diagnostic testing | Neuro-imaging/other investigations | Treatment | Outcome |
|-------------|-------------------|------------------------------------|-----------|---------|
| **Rapidly progressive dementia** | | | | |
| Park et al.[34]/2017 | Repeat scrub typhus antibody titres | MRI=high signal intensity at splenium and subcortical white matter of both hemispheres which resolved on repeat MRI; CSF=normal | Doxycycline | Residual cognitive dysfunction remained even after two months of follow up |
| **Posterior Reversible Encephalopathy Syndrome** | | | | |
| Naveen et al.[35]/2020 | IgM ELISA | MRI suggestive of PRES | Doxycycline and other supportive treatment | Developed seizures requiring levetiracetam and valproate. Patient did not regain consciousness after seizures and died on fifth day of admission due to refractory shock |
| **Cranial neuropathy** | | | | |
| **Optic neuritis** | | | | |
| Jessani et al.[47]/2016 | IgM ELISA | CSF=TLC 60 cells/mm3, 70% lymphocyte, glucose 54 mg/dL. MRI brain/orbit=normal | Doxycycline and IVMP for 5 days | Complete recovery at one month of follow up |
| Cho et al.[48]/2013 | Elevated antibody titre | MRI=bilateral optic neuritis | IV MP for 5 days followed by oral steroid taper | Complete recovery at three months of follow up |
| Bae et al.[49]/2018 | Not mentioned, eschar | MRI=enhancement of the right optic nerve, AQP4-AB + | IV MP 1000 mg for 5 days followed by oral steroid taper | Complete recovery at 4 months; no further treatment taken; no repeat attacks till 5 years |
| **Ophthalmoplegia** | | | | |
| Kim et al.[50]/2015 | Eschar | MRI=anterior cavernous lesion and meningeal thickening; CSF=slightly elevated protein, CSF IgG for scrub typhus elevated | Doxycycline | Complete resolution |
| **Trigeminal neuralgia** | | | | |
| Arai et al.[35]/2007 | Not mentioned | CT brain, CSF normal | Minocycline | Complete resolution |
| Abducens palsy | | | | |
| Ozair et al.[36]/2020 | IgM ELISA positive for scrub, dengue, CKV | MRI brain: leptomeningeal enhancement | Doxycycline | Resolution of LR palsy over months |
| Ete et al.[37]/2016 | IFA IgM | MRI brain, CSF normal | Doxycycline and azithromycin | Improved |
| Bhardwaj et al.[38]/2013 | CSF PCR | MRI brain, CSF normal | Doxycycline | Resolution |
| **Facial palsy** | | | | |
| Lin et al.[39]/2013 | Not mentioned | CSF abnormal; CT brain normal | Doxycycline and intravenous dexamethasone | Partial improvement at 3 months |
| **Hearing loss** | | | | |
| Premaratna et al.[40]/2005 | Rise in antibody titres on IFA | MRI normal | IV chloramphenicol and doxycycline | Complete recovery |
| Kang et al.[41]/2009 | IFA/PCR/Eschar | Not mentioned | Oral tetracycline Chloramphenicol, tetracycline | Hearing improvement over 2 weeks to 3 months |
| Venketesan et al.[42]/2019 | IgM antibody | Not mentioned | Doxycycline | Resolution |

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Table 1: Contd...

| Author/Year         | Diagnostic testing                  | Neuro-imaging/other investigations                          | Treatment                        | Outcome                                      |
|---------------------|--------------------------------------|-----------------------------------------------------------|----------------------------------|----------------------------------------------|
| Nam et al./2010[23] | Elevated serum antibody titres      | CSF cells=49 cells/mm³                                      | Not available                    | Not available                                |
|                     | Elevated antibody titres            | CSF protein=102 mg/dL                                      | Not available                    | Not available                                |
|                     | MRI brain normal in both            |                                                           |                                  |                                              |
| D’sa et al.[39]/2012| IgM ELISA in serum positive for scrub typhus | MRI brain and CSF normal                                  | Doxycycline                      | Complete recovery at 2 weeks                 |
| Koti et al.[39]/2015| IgM Scrub typhus ELISA positive     | MRI brain and CSF normal                                  | Doxycycline                      | Opsoclonus subsided on day 3;4 of treatment and 9th and 10th day of illness |
| Sahu et al./2017    | IgM Scrub typhus ELISA positive     | MRI brain normal; CSF normal                              | Doxycycline and azithromycin    | Opsoclonus decreased 2 days after initiation of therapy and resolved by day 3 |
| Choi et al./2017    | IgM indirect IFA                    | Imaging normal                                            | Doxycycline and steroid IV MP pulse for 5 days | ‘Good’ outcome                              |
| Ralph et al./2019   | Scrub typhus ELISA                  | MRI brain normal; CSF normal                              | Doxycycline + /- azithromycin   | 13/17 followed up at 6 weeks; myoclonus completely resolved in all, opsoclonus persisted in nine. At 3 months, 12 were followed up. Complete resolution of myoclonus in all |
| Sainti et al.[39]/2020 | IgM ELISA                  | MRI brain normal; CSF normal                              | Doxycycline                      | Resolved completely over 7 days              |
| Garg and Dhamija[39]/2021 | IgM ELISA                  | MRI brain and CSF normal; multiorgan dysfunction          | Azithromycin                     | Resolved completely over two weeks          |
| Gupta et al.[39]/2020 | ELISA IgM                  | MRI and CSF normal                                        | Doxycycline                      | Improved over 10 days; residual nystagmus at one month |
| Kaiser et al./2020  | IgM ELISA                          | MRI and CSF normal                                        | Doxycycline                      | Improvement reported                         |
| Bhat et al./2015    | Weil-Felix OXK titre=1:320          | MRI: Diffuse increase in T2/FLAIR signal in cerebellum with swelling | Not mentioned                    | Not mentioned                                |
| Bhoil et al./2016   | Weil-Felix OXK titre=1:320/ IgM ELISA | MRI: cerebelleritis; CSF normal                           | Doxycycline                      | Improvement                                  |
| Didd et al./2017    | IgM ELISA and RT-PCR               | MRI=left focal cerebellar tonsillar hyperintensity        | Doxycycline                      | Resolved in one week                         |
| Karanth et al./2013 | Weil-Felix OXK titre=1:640          | MRI brain normal.                                         | Doxycycline                      | Resolved                                     |
|                     | and IgM ELISA                      | CSF cells 25 mm³, protein 60 mg/dL                       | Doxycycline                      |                                              |
| Mahajan et al./2016 | IgM ELISA                          | MRI=pachymeningeal enhancement, bilateral cerebellar edema | Doxycycline, IV dexamethasone    | Complete resolution at four weeks            |
| Parkinsonism        | Soundararajan et al./2020[25]      | IgM serology                                             | Doxycycline for 14 days         | Complete recovery                            |
|                     | CSF normal                          | Non contrast CT=parietal granuloma                        |                                  |                                              |

Contd...
**Opsoclonus-myoclonus syndrome**

Scrub typhus has been recognised as a para-infectious cause of opsoclonus and/or myoclonus syndrome. First reported by Nam et al. in 2010,[23] it was subsequently described in isolated case reports [Table 1]. The largest data emanate from a retrospective series of 18 cases.[24] In this series, opsoclonus with/without myoclonus was a transient and self-limited phenomenon following onset of fever. All patients had complete resolution at three months of follow-up. The usual onset is in the second week following fever and hence, it is likely to be an immune-mediated phenomenon, although immune modulation seems not to be required for treatment. Neuroimaging is usually normal or may show associated meningeal involvement. CSF may reveal albumino-cytologic dissociation. It is important to recognise scrub typhus as a cause of this often dramatic neurological condition, particularly considering its high amenability to antibiotic therapy alone.

**Cerebellar involvement**

Scrub typhus can rarely cause acute cerebellitis. We identified seven case reports in the literature describing cerebellitis in association with scrub typhus [Table 1]. MRI revealed cerebellar lesions in three of these cases. Most of these patients showed resolution of symptoms with doxycycline alone. Pure cerebellitis in the absence of meningitis may also occur, as reported in four cases.[25-28] In this latter context, acute cerebellar ataxia due to Plasmodium falciparum malaria forms an important differential in tropical regions.

**Parkinsonism**

Parkinsonism is also uncommonly reported in scrub typhus. Three individual case reports have described parkinsonism occurring during the course of scrub typhus with complete improvement following initiation of doxycycline. Imaging (CT/MRI) was normal in all these patients. In two of these cases, myoclonus was associated with parkinsonism. This co-occurrence of myoclonus and parkinsonism has also been noted in a case series reported from southern India focussed on delineating details of opsoclonus in scrub typhus, suggesting a shared immunological mechanism. Of 18 patients with opsoclonus in this retrospective series, 6 (33%) were noted to have associated parkinsonism.[24] Although this completely resolved in five, persistent asymmetrical extrapyramidal features were noted in one patient at 12 weeks of follow-up. Whether Parkinson disease was uncovered by scrub typhus or triggered by it in this patient remains conjectural.

**Transverse myelitis**

Four patients with acute transverse myelitis have been reported. The onset of symptoms ranged from 4 to 14 days after onset of fever. MRI variably showed cervical, dorsal and lumbar cord enhancement and swelling. All patients were managed with steroids in conjunction with doxycycline. In one patient, initial doxycycline therapy alone was insufficient to stimulate improvement, prompting the clinicians to initiate steroids, triggering recovery. This favours an immunological basis underlying this presentation in scrub typhus. The grey matter

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**Table 1: Contd...**

| Author/Year | Diagnostic testing | Neuro-imaging/other investigations | Outcome | Treatment |
|-------------|--------------------|------------------------------------|---------|-----------|
| Ralph et al.[24]/2019 | IgM ELISA | Normal brain and EEG | Complete improvement | Doxycycline, amantadine, clonazepam |
| Premartha et al.[25]/2013 | Indirect IFA | MRI normal | Improved at one-year follow-up | Doxycycline, +/− azithromycin |
| Chou et al.[26]/2013 | IgM ELISA | MRI normal | Not available | Doxycycline and steroids |
| Ryu et al.[27]/2017 | Indirect IFA | MRI normal | Near normal power at three months | Doxycycline and steroids |
| Yun et al.[28]/2017 | IgM ELISA | MRI normal | Improved at one-year follow-up | Doxycycline, +/− azithromycin |
| Lee et al.[29]/2008 | Presence of typical eschaton | MRI on MT=4 D11 | Complete improvement | Doxycycline, +/− azithromycin |

IgM ELISA: Immunoglobulin M enzyme-linked immunosorbent assay; Indirect IFA: Indirect immunofluorescence assay; Doxycycline: Doxycycline; Azithromycin: Azithromycin; MRI: Magnetic resonance imaging; MT: Magnetic resonance tomography; SF: Serum ferritin; NMO: Neuromyelitis optica; IFA: Indirect immunofluorescence assay; ATM: Acute transverse myelitis; CKV: Chikungunya virus; CSF: Cerebrospinal fluid; CT: Computed tomography; ERP: Electroencephalography; EPS: Extrapyramidal syndrome; F: Female; GCS: Glasgow coma scale; M: Male; MP: Methyl prednisolone; NMO: Neuromyelitis optica; PCR: Polymerase chain reaction; SD: Standard deviation.

Scrub typhus can rarely cause acute cerebellitis. We identified seven case reports in the literature describing cerebellitis in association with scrub typhus [Table 1]. MRI revealed cerebellar lesions in three of these cases. Most of these patients showed resolution of symptoms with doxycycline alone. Pure cerebellitis in the absence of meningitis may also occur, as reported in four cases.[25-28] In this latter context, acute cerebellar ataxia due to Plasmodium falciparum malaria forms an important differential in tropical regions.
Table 2: Peripheral nervous system involvement in scrub typhus other than meningitis/encephalitis

| Author/Year | Country | Type of study | Number of cases | Age (years) | Sex | Onset of neurological illness after fever (days) |
|-------------|---------|---------------|-----------------|-------------|-----|-----------------------------------------------|
| Brachial plexopathy | | | | | | |
| Ting et al.[36]/1992 | Taiwan | Case report | Fever, headache, pneumonia | 20 | M | Not reported |
| Banda et al.[37]/2016 | India | Case report | Fever and right shoulder pain; difficulty in raising right arm | 45 | F | 5 |
| Radiculopathy/Radiculoneuropathy | | | | | | |
| Dev et al.[38]/2019 | India | Case report | Leptospirosis and scrub typhus co-infection | 20 | M | 8 |
| Muranjan and Karande[39]/2017 | India | Case report | Fever, vomiting, irritability, paraparesis | 13 months | M | 3 |
| Gangula et al.[40]/2017 | India | Case report | Mixed infection with P. falciparum and scrub typhus | 40 | M | 10 |
| Sawale et al.[41]/2014 | India | Case report | Fever, rash, eschar-treated with doxycycline and defervesced. Four days later, developed flaccid quadriparesis | 41 | M | 15 |
| Ju et al.[42]/2011 | Korea | Case series | 1. Headache, fever treated with doxycycline-developed lower limb weakness on treatment 2. Fever, myalgia, presented in diabetic ketoacidosis. Quadriparesis noted on examination. | 60 | M | 10 |
|  | | | | 46 | F | 7 |
| Sakai et al.[43]/2016 | Japan | Case series | 1 | 66 | M | 7 |
| Lee SH et al.[44]/2007 | Korea | Case series | 1. Fever which defervesced with doxycycline. Developed quadriparesis after discharge. | 42 | F | 14 |
| Lee MS et al.[45]/2009 | Korea | Case report | 1. Fever followed by quadriparesis and facial palsy 2. Chills, myalgia followed by quadriparesis and facial weakness | 54 | M | 16 |
|  | | | | 74 | F | 8 |
| Miller Fisher syndrome | | | | | | |
| Kim et al.[46]/2014 | Korea | Case report | Fever followed by facial palsy and bilateral ptosis | 70 | M | 14 |
|  | | | | | | |
| Mononeuritis multiplex | | | | | | |
| Hayakawa et al.[47]/2012 | Japan | Case report | Fever, vomiting, abdominal pain due to acalculous cholecystitis. Developed right hand hypesthesia and of both lower extremities. Eschar present. | 72 | F | 12 |
| Muscle involvement | | | | | | |
| Ki et al.[48]/2018 | Korea | Case report | 1 | 54 | F | Not reported |
| Kalita et al.[49]/2015 | India | Case report | 33 patients=13 had muscle involvement | Median age: 32 years (range 15-70 years) | 61% males | Median :15 Range: 4-30 days |
| Young et al.[50]/2003 | Korea | Case report | Fever, diffuse myalgia and muscle weakness | 71 | F | Not reported |
| Multi-axial involvement [Central plus Peripheral Nervous System] | | | | | | |
| Kim et al.[51]/2008 | Korea | Case report | Peripheral neuropathy plus stroke | 64 | M | Not reported |
| Himral et al.[52]/2019 | India | Case report | Multiple cranial nerve palsies and cerebellitis | 24 | F | 4 |
| Tandon et al.[53]/2019 | India | Case report | Myelitis, meningoencephalitis, and axonal polyneuropathy | 17 | M | 4 |
| Phillips et al.[54]/2018 | India | Case report | Meningoencephalitis and GBS | 70 | M | 5 |

Author/Year | Diagnostic test for scrub typhus | Neuroimaging/other investigations | Treatment | Outcomes reported |
|-------------|--------------------------------|---------------------------------|-----------|------------------|
| Brachial plexopathy | | | | |
| Ting et al.[36]/1992 | Weil-Felix/IFA | Electrophysiology suggestive of brachial plexus neuropathy | Not known | Substantial recovery |

Contd...
Table 2: Contd...

| Author/Year          | Diagnostic test for scrub typhus                                                                 | Neuroimaging/other investigations                                      | Treatment                                                                 | Outcomes reported                                      |
|----------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|
| Banda et al.[37]/2016 | ELISA and PCR                                                                                   | NCS suggestive of brachial neuritis                                     | Doxycycline for 10 days                                                 | Pain and weakness resolved                             |
|                     | Radiculopathy/Radiculoneuropathy                                                                |                                                                         |                                                                         |                                                        |
| Dev et al.[39]/2019  | ELISA for scrub and microagglutination for Leptospira Both confirmed by PCR                      | NCS=demyelinating                                                      | Doxycycline, cephalosporin, other supportive measures                    | Rapid recovery over 10 days                           |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Muranjan and Karande[43]/2017 | Weil-Felix and ELISA                                                                 | MRI=hydrocephalus and meningeal enhancement; CSF=5 neutrophils/mm³, 13 lymphocytes/mm³, protein 77 mg/dL, sugar 37 mg/dL. NCS/EMG suggestive of lumbosacral radiculopathy | Chloramphenicol for 10 days                                           | Complete improvement at 2 months                       |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Gangula et al.[37]/2017 | ELISA IgM                                                                                       | NCS=demyelinating                                                      | Doxycycline, artesunate, antibiotics, primaquine                         | Gradual improvement                                   |
|                     |                                                                                                 | Blood smear: gametocyte of Plasmodium falciparum                       |                                                                         |                                                        |
| Sawale et al.[76]/2014 | Solid phase immunochromatographic assay antigen positive for scrub typhus                      | NCS=Demyelinating neuropathy with absent F waves, CSF showed albumino cytological dissociation | Five cycles of plasmapharesis given                                    | Gradual improvement                                   |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Ju et al.[37]/2011   | Serum O. tsutsugamushi titre + Serum O. tsutsugamushi titre +                                   | NCS=demyelinating                                                      | IVIg+doxycycline                                                        | Improved                                               |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Sakai et al.[80]/2016 | IgM ELISA                                                                                       | NCS=Acute sensorimotor polyneuropathy                                   | IV Ig                                                                  | Improved                                               |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Lee SH et al.[76]/2007 | IgM ELISA                                                                                      | NCS=axonal                                                             | IV Ig                                                                  | Improvement                                            |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Lee MS et al.[80]/2009 | Indirect IFA                                                                                   | NCS=demyelinating                                                      | IV Ig                                                                  | Improved                                               |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Miller Fisher syndrome |                                                                                               | NCS=demyelinating                                                      | IV Ig                                                                  | Improved                                               |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Kim et al.[80]/2014  | ELISA                                                                                           | NCS=Reduced SNAPs, absent H reflexes                                    | IV Ig for 5 days (had previously received doxycycline)                  | Gradual recovery                                       |
|                     | Anti-GQ1b antibodies negative                                                                  |                                                                         |                                                                         |                                                        |
| Mononeuritis multiplex |                                                                                               |                                                                         |                                                                         |                                                        |
| Hayakawa et al.[81]/2012 | Indirect IFA                                                                                 | NCS=mononeuritis multiplex                                             | Minocycline 100 mg twice daily for 10 days                              | Improved                                               |
| Muscle involvement   |                                                                                                 |                                                                         |                                                                         |                                                        |
| Ki et al.[82]/2018   | Presence of eschar; Indirect IFA                                                                | CPK=3337 U/L; Increased to 18,262 U/L; myocarditis                     | Doxycycline                                                            | Complete recovery                                      |
|                     | Immuno-chromatographic assay of scrub typhus antibodies and/or a positive Weil-Felix test       | CPK levels ranged between 287-3166 U/L                                 | Doxycycline                                                            | Complete clinical recovery and normalisation of CPK levels at one month |
|                     |                                                                                                 | EMG=short duration polyphasic potentials                               |                                                                         |                                                        |
| Young et al.[83]/2003 | Indirect IFA                                                                                   | CPK=3250 U/L, deranged KFT; dark brown urine                           | Doxycycline                                                            | Complete recovery                                      |
|                     |                                                                                                 | Muscle biopsy=evidence of vasculitis                                    |                                                                         |                                                        |
| Multi-axial involvement [Central plus Peripheral Nervous System] |                                                                                               |                                                                         |                                                                         |                                                        |
| Kim et al.[84]/2008  | Serum indirect IFA positive                                                                    | MRI=multiple infarcts; NCS=demyelinating neuropathy; bilateral sensorineural deafness | Doxycycline                                                            | Improvement in NCS and audiometry findings at 3 months |
|                     |                                                                                                 |                                                                         |                                                                         |                                                        |
| Himral et al.[85]/2019 | IgM ELISA                                                                                       | MRI=right frontoparieto temporal region, right thalamus, left temporal lobe, bilateral cerebellar hemispheres | Doxycycline                                                            | Improvement                                            |
of the spinal cord has been noted to have a specific predilection to be affected, which may be attributable to the high metabolic demands of spinal cord grey matter.

Encephalomyelitis

Two cases of acute encephalomyelitis have been reported in association with scrub typhus. Both patients developed obtundation and quadriparesis accompanied by sixth and/or seventh cranial nerve involvement. One patient was treated with steroids apart from doxycycline but did not respond well. The second patient showed favourable response to doxycycline therapy alone.

Status epilepticus

Although seizures have been reported in 6.3–21.6% of patients with scrub typhus, status epilepticus (SE) is reported less commonly. In one study, 13 out of 66 (19.7%) patients with scrub typhus admitted to a tertiary centre in northern India had SE. All responded to antiseizure medications (ASMs) and scrub typhus treatment. ASMs could be stopped within one year in all patients as all had normal MRI and resolution of EEG abnormalities. Non‑convulsive SE has been reported in one patient with scrub meningo‑encephalitis.

Other central nervous system manifestations

Scrub typhus has been implicated as a cause of rapidly progressive cognitive impairment in one report. However, causality was uncertain in this case report, as baseline cognitive status of the patient prior to acute deterioration was uncertain. Cognitive issues persisted despite improvement in neuroimaging features after treatment for scrub typhus. In another case report, the development of posterior reversible encephalopathy syndrome (PRES) was also attributed to scrub typhus treatment. In one patient with PRES, a precipitous decline in blood pressure was noted. Glasgow Coma Scale declined from 15 to 8. Nerve conduction studies revealed normal sensory and motor nerve conduction velocities. Magnetic resonance imaging of the brain showed hypointense lesions in the posterior parietal and occipital regions. Intravenous immunoglobulins were administered. However, there was no resolution of cognitive issues. The patient was discharged on oral medications.

Peripheral nervous system involvement in scrub typhus

Plexus involvement

We found 11 reports of plexus involvement in scrub typhus. The age ranged from 13 months to 74 years. The range of duration from onset to weakness was 3–16 days. Nerve conduction studies revealed both demyelinating and axonal patterns. There was one report of Miller Fisher syndrome. All patients showed improvement with intravenous immunoglobulins. The age ranged from 13 months to 74 years. The range of duration from onset to weakness was 3–16 days. Nerve conduction studies revealed both demyelinating and axonal patterns. There was one report of Miller Fisher syndrome.

Radiculoneuropathy

We found 11 reports of acute radiculoneuropathy in association with scrub typhus. The age ranged from 13 months to 74 years. The range of duration from onset to weakness was 3–16 days. Nerve conduction studies revealed both demyelinating and axonal patterns. There was one report of Miller Fisher syndrome. All patients showed improvement with intravenous immunoglobulins. The age ranged from 13 months to 74 years. The range of duration from onset to weakness was 3–16 days. Nerve conduction studies revealed both demyelinating and axonal patterns. There was one report of Miller Fisher syndrome.


doxycline therapy

CPK=Creatine phosphokinase; CSF=cerebrospinal fluid; F=female; EMG=Electromyography; GBS=Guillain–Barre syndrome; IVIg=Intravenous immunoglobulin; IFA=Indirect immunofluorescence assay; M=male; MRI=magnetic resonance imaging; NCS=Nerve conduction studies; PCR=Polymerase chain reaction.
Peripheral neuropathy
One patient with mononeuritis multiplex developing in association with scrub meningitis and acalculous cholecystitis has been reported.[81] This patient was managed with minocycline for 10 days with complete response.

Muscle involvement[82‑84]
In one case series, 13 of 33 (39%) patients were noted to have muscle involvement, in the form of myalgia or muscle weakness, in combination with elevated CPK levels [Table 2].[83] All these patients reported severe and generalised myalgia. They had moderately elevated creatine phosphokinase (CPK) levels ranging from 287‑3166 U/L. The electromyographic findings demonstrated short-duration polyphasic potentials. Muscle biopsy exhibited features of vasculitis. Treatment with doxycycline led to improvement in clinical symptoms as well as CPK levels.

In one other case report, myalgias and high CPK levels were associated with rhabdomyolysis and in another report, severe myocarditis accompanied muscle involvement.[82,84] Both patients showed complete resolution with doxycycline alone.

Despite the demonstration of vasculitis on muscle biopsy in the series by Kalita et al., immunomodulation in terms of steroids seems not to be necessary for the management of myositis.[83]

Multi‑axial involvement
Several case reports describe simultaneous or tandem involvement of central and peripheral nervous system including peripheral neuropathy/Guillain–Barre syndrome with stroke/myelitis/meningoencephalitis, multiple cranial nerve palsies and cerebellitis.[85‑88]

Diagnostic issues
The mainstay of diagnosis in scrub typhus is via serological testing.[89] In primary scrub typhus, IgM antibodies usually develop by the end of the first week and IgG antibodies develop by the second week. The diagnosis of scrub typhus among the reports included in this review included mainly Weil‑Felix test, enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescent antibody (IFA) test. Since these tests are associated with nuances and pitfalls, it is essential to discuss their importance in the context of diagnosis of scrub typhus.

Since O. tsutsugamushi is an intracellular pathogen, it cannot be isolated through standard bacterial culture but requires cell culture. Hence, nucleic acid amplification tests form the mainstay of diagnosis. Weil‑Felix test is the oldest diagnostic test available, and it is based on cross‑reaction with proteus OXK strain. It is, however, hindered by low sensitivity and cross reacts with other rickettsial agents. IFA is considered to be the diagnostic gold standard. This test detects the presence of antibodies in the sera of infected individuals that bind to immobilised antigen, using fluorescein labelled anti‑human immunoglobulin. IFA requires demonstration of four‑fold rise in antibody titre in acute and convalescent phase sera, and no absolute value can be used for diagnosis. ELISA is frequently used, as it is widely available and requires less technical input compared to IFA. The antigen used is a 56 kDa antigen which combines with IgM antibodies against Karp, Kato, Gilliam and TA716 strains in acute infection. Immunochromatographic tests are rapid point‑of‑care tests, which also use the 56 kDa antigen of Karp, Kato and Gilliam strains and have variable sensitivity and specificity. Polymerase chain reaction (PCR) directly detects the organism with high sensitivity and specificity, even at low copy numbers. However, cost is a prohibitive element, especially in low‑resource settings. In the studies included in the review, the diagnosis was made on the basis of ELISA in the majority of patients, followed by IFA. ELISA has very high sensitivity of 92%‑97% and specificity of 94%‑99%.[89] A false positive may arise with other acute febrile illnesses, such as dengue, leptospirosis and spotted fever. A purely clinical diagnosis, hinging on the presence of an eschar was made in a handful. Eschar, if present, has high specificity (98.9%), but its presence may be highly variable among patients.

Treatment considerations
Doxycycline (100 mg twice daily, oral/intravenous) is the treatment of choice. Azithromycin is an alternative agent. Most of the neurological manifestations of scrub typhus, including meningitis, encephalitis, myositis, cerebellar dysfunction responded to these antibiotics. However, some of those with an immune pathogenesis, such as transverse myelitis, Guillain–Barre syndrome and optic neuritis, required treatment with steroid therapy or intravenous immunoglobulins. It is noteworthy that even neurological features with likely immune mechanisms were reported to respond to antibiotic therapy alone, without the need for steroids, as in several cases of opsoclonus myoclonus, cerebellar dysfunction and parkinsonism. Other antibiotic treatment options include chloramphenicol, rifampicin and tetracycline.

Conclusions
Our review informs comprehensive detailing of neurological facets related to scrub typhus described till date. Information was gleaned from individual case reports, case series, retrospective and prospective data. The pathogenesis of this wide array of manifestations is also unclear, and probably multifactorial. Among the most important observations is that most of these neurological manifestations respond exceedingly well to doxycycline or other appropriate antibiotics. Only few immune‑mediated conditions such as post‑infectious optic neuritis, cerebellitis, Guillain–Barre syndrome required immune therapy in the form of steroids. Other dramatic clinical conditions including opsoclonus‑myoclonus, meningitis/encephalitis, and even ADEM responded promptly to antibiotic therapy. Or review highlights that scrub typhus must be enlisted high in the differential diagnosis list among patients in endemic areas presenting with acute febrile illness, especially in the setting of multi‑organ dysfunction and presence of an eschar due to its eminently treatable yet potentially lethal nature.
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