Neurological Facets of Scrub Typhus: A Comprehensive Narrative Review

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Abstract

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.[1] However, reports have also emerged from other regions such as South America and Africa, lately.[2] Above one billion individuals are at risk for scrub typhus in endemic areas.[3] 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.[4] 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).[5] 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.[5-88] 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 opsoclonus, myoclonus, GBS and myelitis.

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

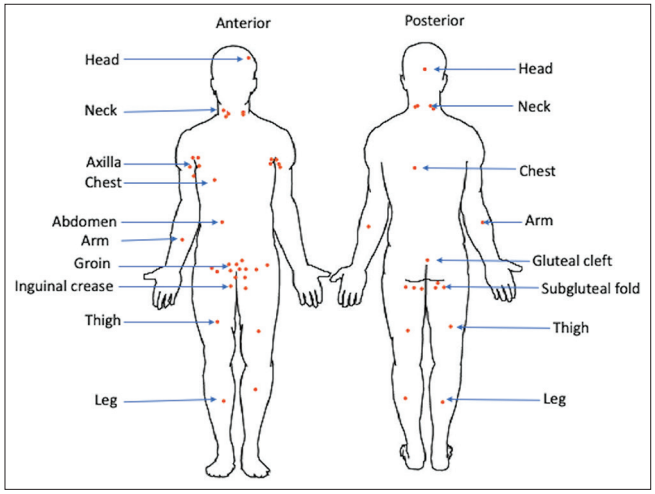

Figure 1: Sites of distribution of eschar of scrub typhus on the human body

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, opsoclonus, 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

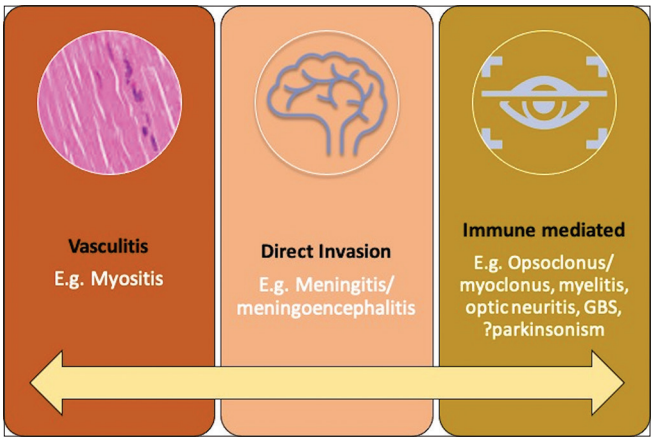

Figure 2: Pathogenesis of neurological features of scrub typhus

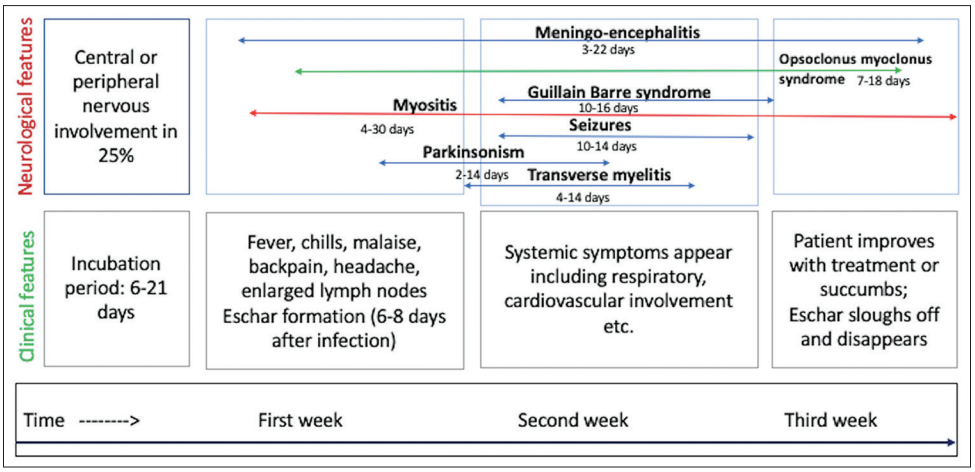

Figure 3: Timelines of evolution of neurological manifestations in scrub typhus

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
Meningitis/Encephalitis						
Lee *et al.*[15]/2017	Korea	Retrospective case series	16	35.5	62.5% F	3-22
Dhanapriya *et al.*[39]/2017	India	Case report	Fever, chills, headache, vomiting in a renal transplant recipient	45	F	6
Sharma *et al.*[40]/2015	India	Prospective case series	23	Range: 19-68 years	56.5% 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	9.4±3
Misra *et al.*[5]/2015	India	Cross-sectional	37	3-71	49	Not reported
Boorugu *et al.*[9]/2014	India	Prospective case series	189	Not reported	Not reported	Not reported
Kar *et al.*[43]/2014	India	Prospective case series	6	35-62	5/6 males	2-4 (mean 3)
Viswanathan *et al.*[44]/2013	India	Retrospective case series	17/65 had meningitis	41.8+17.7	33 M/32 F	Not reported
Kim *et al.*[45]/2013	Korea	Case-control study	22	70	63.6% F	Not reported
Khan *et al.*[12]/2017	India	Retrospective case series	104/511 AES cases had scrub typhus	Median age 25	55.7% males	Not reported
Gaba *et al.*[46]/2020	India	Case report	Fever with chills followed by headache, vomiting, stupor	19	F	4
Mahajan *et al.*[28]/2016	India	Retrospective	44/253 (17.4%)	41.4+31.7	69.6% F	Not mentioned
Encephalomyelitis						
Chen *et al.*[30]/2006	Taiwan	Case report	Fever, altered sensorium, dysarthria and left hemiparesis, seizure, left facial paresis	77	M	10
Kim *et al.*[31]/2000	Korea	Case report	Headache, fever, vomiting, drowsiness followed by dysarthria and quadriparesis, bilateral abducens palsies, facial paralysis	22	F	5
Status epilepticus						
Kalita *et al.*[33]/2021	India	Case report	Fever, persistent altered sensorium	50	F	Simultaneous
Kalita *et al.*[32]/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.*[34]/2017	Korea	Case report	Acute cognitive impairment with reversible splenial lesions	78	F	Not specified
Posterior Reversible Encephalopathy Syndrome						
Naveen *et al.*[35]/2020	India	Case report	Fever followed by headache, hypotension, seizure and obtundation	40	F	4
Cranial neuropathy						
Optic neuritis						
Jessani *et al.*[47]/2016	India	Case report	Fever, headache, right eye pain and visual loss	8	F	Not reported
Cho *et al.*[48]/2013	Korea	Case report	Bilateral loss of vision two weeks after resolution of febrile illness	8	M	21
Bae *et al.*[49]/2018	Korea	Case report	Post-infectious ON with NMO+	82	F	21

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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
Ophthalmoplegia						
Kim *et al.*[50]/2015	Korea	Case report	Fever followed by ptosis and ophthalmoplegia	69	M	5
Trigeminal neuralgia						
Arai *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	1. 47-5. 57-58 6.52	F F F	14 12-15 9
Kang *et al.*[56]/2009	Korea	Case series	4 (Patients 2,3 had otalgia without hearing loss)	1. 60 2-4. Not mentioned	F Not mentioned	10 Not reported
Venketesan *et al.*[57]/2019	India	Case report	Loin pain, dysuria, fever, hearing loss in a diabetic	52	F	Not mentioned
Opsoclonus and/or myoclonus						
Nam *et al.*/2010[23]		Case reports	2	64 40	F M	Not mentioned Not mentioned
D'sa *et al.*[58]/2012	India	Case report	Fever, headache, oscillopsia	54	M	5
Koti *et al.*[59]/2015	India	Case report	Fever, dyspnea, restlessness followed by opsoclonus myoclonus	26	M	6
Sahu *et al.*[60]/2017	India	Case report	Fever, ataxia, tremulousness, pancerebellar syndrome, opsoclonus	60	M	3
Choi *et al.*[61]/2017	Korea	Case report	Fever, rash, tremors, parkinsonism	59	M	8
Ralph *et al.*[24]/2019	India	Case series	18 patients in a retrospective series had opsoclonus, of which 9 (50%) had myoclonus associated	-	-	Mean 11 days (range 7-18 days)
Saini *et al.*[62]/2020	India	Retrospective case series	1 had scrub typhus in this series of children with 'infection-associated opsoclonus'	7	F	5
Garg and Dhamija[63]./2021	India	Case report	Abnormal eye and limb movement, fever	23	F	7
Cerebellar dysfunction						
Gupta *et al.*[25]/2020	India	Case report	Fever for 4 days followed by pan-cerebellar symptoms	26	F	5

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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, pancerebellar involvement	21	M	3
Didel *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.*/2020[67]	India	Case report	Fever, cough, dyspnoea, slurred speech, ret tremor, hypomimia, hypophonia	50	M	14
Ralph *et al.*[24]/2019	India	Case series reporting on opsoclonus in scrub typhus	6/18 (33%) had EPS	-	-	-
Premaratna *et al.*[68]/2015	Sri Lanka	Case report	Fever, right sided rest tremors, stiffness right leg	62	M	5
Chiou *et al.*[69]/2013	Taiwan	Case report	Fever, rash, rigidity, myoclonus, tremors	55	M	2
Transverse myelitis						
Ryu *et al.*[70]/2020	Korea	Case report	Fever, headache; responded to doxycycline; then developed sudden paraparesis with bowel and bladder involvement	66	M	7
Yun *et al.*[29]/2017	Korea	Case report	Fever, chills followed by ascending paraparesis (power grade 2/5)	67	M	14
Mahajan *et al.*[71]/2016	India	Case report	Fever, chills, headache, paraparesis	35	F	4
Lee *et al.*[72]/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
Meningitis/Encephalitis				
Lee *et al.*[15]/2017	Indirect IFA	MRI: leptomeningeal enhancement in 4 patients; abnormal CSF in 13/16	Doxycycline with/without clarithromycin/azithromycin	15/16=improved completely 1/16=persistent facial palsy
Dhanapriya *et al.*[39]/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.*[40]/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.*[41]/2015	CT/MRI normal; Mean CSF cells 152 + 67 cells/mm^3, 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/mm^3; 98.66±3.09% L	Tablet doxycycline with or without injection azithromycin	2/13 (15%) died; both has multi organ dysfunction.

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Table 1: Contd...

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/mm^3 (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.*[5]/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	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.*[45]/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.*[12]/2017	IgM ELISA	-	-	53/104 patients could be followed up; 26 died after discharge
Gaba *et al.*[46]/2020	IgM ELISA RT-PCR	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.*[28]/2016	IgM ELISA	18/44 had abnormal CSF	Doxycycline/azithromycin	Altered sensorium risk factor for mortality
Encephalomyelitis				
Chen *et al.*[30]/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/mm^3, glucose 41 mg/dL, protein 219 mg/dL	No response to minocycline; Intravenous high dose corticosteroids	Developed coma and quadriparesis 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 epilepticus				
Kalita *et al.*[33]/2021	IgM ELISA	MRI brain normal; EEG =>2.5 hertz generalised epileptiform discharges; CSF abnormal	Lorazepam, valproate, levetiracetam Doxycyline	Complete recovery
Kalita *et al.*[32]/2016	Solid phase immuno chromatography 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=mildly elevated protein, CSF IgG for scrub typhus elevated	Doxycycline	Complete resolution
Trigeminal neuralgia				
Arai *et al.*[51]/2007	Not mentioned	CT brain, CSF normal	Minocycline	Complete resolution
Abducens palsy				
Ozair *et al.*[20]/2020	IgM ELISA positive for scrub, dengue, CKV	MRI brain: leptomeningeal enhancement	Doxycycline	Resolution of LR palsy over months
Ete *et al.*[52]/2016	IFA IgM	MRI brain, CSF normal	Doxycycline and azithromycin	Improved
Bhardwaj *et al.*[53]/2013	CSF PCR	MRI brain, CSF normal	Doxycycline	Resolution
Facial palsy				
Lin *et al.*[54]/2013	Not mentioned	CSF abnormal; CT brain normal	Doxycycline and intravenous dexamethasone	Partial improvement at 3 months
Hearing loss				
Premaratna *et al.*[55]/2005	Rise in antibody titres on IFA Rise in antibody titres on IFA IgM antibodies	MRI normal	IV chloramphenicol and doxycycline Oral tetracycline Chloramphenicol, tetracycline	Complete recovery Hearing improvement over 2 weeks to 3 months Patient died 48 hours after admission
Kang *et al.*[56]/2009	IFA/PCR/Eschar Not reported	Not mentioned	Not reported	Resolution
Venketesan *et al.*[57]/2019	IgM antibody	Not mentioned	Doxycycline	Hearing improved

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Table 1: Contd...

Author/Year	Diagnostic testing	Neuro-imaging/other investigations	Treatment	Outcome
Opsoclonus and/or myoclonus				
Nam *et al.*/2010[23]	Elevated serum antibody titres	CSF cells=49 cells/mm^3	Not available	Not available
		CSF protein=102 mg/dL	Not available	Not available
	Elevated antibody titres	CSF cells=28 cells/mm^3		
		CSF protein=91 mg/dL		
		MRI brain normal in both		
D'sa *et al.*[58]/2012	IgM ELISA in serum positive for scrub typhus	MRI brain and CSF normal	Doxycycline	Complete recovery at 2 weeks
Koti *et al.*[59]/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.*[60]/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.*[61]/2017	IgM indirect IFA	Imaging normal	Doxycycline and steroid IV MP pulse for 5 days	'Good' outcome
Ralph *et al.*[24]/2019	Scrub typhus ELISA	14/18 patients had abnormal CSF (2 were not tested)	Doxycycline +/- azithromycin	13/17 followed up at 6 weeks; myoclonus completely resolved in all, opsoclonus persisted in nine.
		Normal MRI in 9/12 patients		At 3 months, 12 were followed up. Complete resolution of myoclonus in all
Saini *et al.*[62]/2020	IgM ELISA	MRI brain normal	Doxycycline	Resolved completely over 7 days
		CSF showed 30 cells/m^3, 55 mg/dL protein		
Garg and Dhamija[63]./2021	IgM ELISA	MRI and CSF normal; multiorgan dysfunction	Azithromycin	Resolved completely over two weekd
Cerebellar dysfunction				
Gupta *et al.*[25]/2020	ELISA IgM	MRI and CSF normal	Doxycycline	Improved over 10 days; residual nystagmus at one month
Kaiser *et al.*[64]/2020	IgM ELISA	CSF: 102 cells/mm^3, 92% mononuclear, glucose -59 mg/dL, protein 119 mg/dL	Doxycycline	Improvement reported
Bhat *et al.*[65]/2015	Weil-Felix OXK titre=1:320	MRI: Diffuse increase in T2/FLAIR signal in cerebellum with swelling	Not mentioned	Not mentioned
		CSF: not done		
Bhoil *et al.*[26]/2016	Weil-Felix OXK titre=1:320/ IgM ELISA	MRI: cerebellitis; CSF normal	Doxycycline	Improvement
Didel *et al.*[66]/2017	IgM ELISA and RT-PCR	MRI=left focal cerebellar tonsillar hyperintensity	Doxycycline	Resolved in one week
Karanth *et al.*[27]/2013	Weil-Felix OXK titre=1:640	MRI brain normal.	Doxycycline	Resolved
	and IgM ELISA	CSF cells 25/mm^3, protein 60 mg/dL		
Mahajan *et al.*[28]/2016	IgM ELISA	MRI=pachymeningeal enhancement, bilateral cerebellar edema	Doxycycline, IV dexamethasone	Complete resolution at four weeks
		CSF=15 lymphocytes, protein 90 mg/dL, sugar 52 mg/dL		
Parkinsonism				
Soundararajan *et al.*/2020[67]	IgM serology	CSF normal	Doxycycline for 14 days	Complete recovery
		Non contrast CT=parietal granuloma		

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Table 1: Contd...

Author/Year	Diagnostic testing	Neuro-imaging/other investigations	Treatment	Outcome
Ralph *et al.*[24]/2019	IgM ELISA	Details not available	Doxycycline + /- azithromycin	Recovery in all except one patient who had persisting EPS at 3 months
Premaratna *et al.*[68]/2015	IgM ELISA	Normal CT brain and EEG	Oral doxycycline and azithromycin	Parkinsonism resolved over two weeks
Chiou *et al.*[69]/2013	IgM ELISA	MRI normal	Doxycycline, amantadine, clonazepam	Improvement in parkinsonism and myoclonus
Transverse myelitis				
Ryu *et al.*[70]/2020	Indirect IFA	Dorso-lumbar cord hyperintensity	Steroid pulse for 5 days	Improved at one-year follow up
Yun *et al.*[29]/2017	Indirect IFA	Swelling of cervicodorsal cord with grey matter involvement	Doxycycline led to no response in ATM. This was followed by pulse steroids, oral steroids	Near normal power at three months
Mahajan *et al.*[71]/2016	IgM ELISA	LETM on MRI- C4-D11	Doxycycline IV MP followed by oral steroids	Weakness improved but had residual bladder complaints at one year
Lee *et al.*[72]/2008	Presence of typical eschar	T1-T3 increased signal intensity/enhancement Normal CT brain, CSF	Doxycycline and steroids	Not available

ATM=Acute transverse myelitis; CKV=Chikungunya virus; CSF=Cerebrospinal fluid; CT=Computed tomography; EEG=Electroencephalography; EPS=Extrapyramidal syndrome; F=female; GCS=Glasgow coma scale; IFA=Indirect immunofluorescence assay; IV=intravenous; LETM=Longitudinally extensive transverse myelitis; M=male; MP=methyl prednisolone; MRI=magnetic resonance imaging; NMO=Neuromyelitis optica; AQP4=Aquaporin 4; PCR=Polymerase chain reaction; SD=Standard deviation

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

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, pneumonitis	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*.[73]/2019	India	Case report	Leptospirosis and scrub typhus co-infection	20	M	8
Muranjan and Karande[74]/2017	India	Case report	Fever, vomiting, irritability, paraparesis	13 months	M	3
Gangula *et al*.[75]/2017	India	Case report	Mixed infection with P. falciparum and scrub typhus	40	M	10
Sawale *et al*.[76]/2014	India	Case report	Fever, rash, eschar-treated with doxycycline and defervesced. Four days later, developed flaccid quadriparesis	41	M	15
Ju *et al*.[77]/2011	Korea	Case series	1. Headache, fever- treated with doxycycline- developed lower limb weakness on treatment	60	M	10
			2. Fever, myalgia, presented in diabetic ketoacidosis. Quadriparesis noted on examination.	46	F	7
Sakai *et al*.[78]/2016	Japan	Case series	1	66	M	7
			2	58	F	15
Lee SH *et al*.[79]/2007	Korea	Case series	1. Fever which defervesced with doxycycline. Developed quadriparesis after discharge.	42	F	14
Lee MS *et al*.[80]/2009	Korea	Case reports	1. Fever followed by quadriparesis and facial palsy	54	M	16
			2. Chills, myalgia followed by quadriparesis and facial weakness	74	F	8
Miller Fisher syndrome						
Kim *et al*.[38]/2014	Korea	Case report	Fever followed by facial palsy and bilateral ptosis	70	M	14
Mononeuritis multiplex						
Hayakawa *et al*.[81]/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*.[82]/2018	Korea	Case report	1	54	F	Not reported
Kalita *et al*.[83]/2015	India	Case series	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*.[84]/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*.[85]/2008	Korea	Case report	Peripheral neuropathy plus stroke	64	M	Not reported
Himral *et al*.[86]/2019	India	Case report	Multiple cranial nerve palsies and cerebellitis	24	F	4
Tandon *et al*.[87]/2019	India	Case report	Myelitis, meningoencephalitis, and axonal polyneuropathy	17	M	4
Phillips *et al*.[88]/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

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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*.[73]/2019	ELISA for scrub and microagglutination for Leptospira Both confirmed by PCR	NCS=demyelinating	Doxycyline, cephalosporine, other supportive measures	Rapid recovery over 10 days
Muranjan and Karande[74]/2017	Weil-Felix and ELISA	MRI=hydrocephalus and meningeal enhancement; CSF=5 neutrophils/mm^3, 13 lymphocytes/mm^3, 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*.[75]/2017	ELISA IgM	NCS=demyelinating Blood smear: gametocyte of Plasmodium falciparum	Doxycycline, artesunate, antibiotics, primaquine	Gradual improvement
Sawale *et al*.[76]/2014	Solid phase immunochromatographic assay antibody positive for scrub typhus	NCS=Demyelinating neuropathy with absent F waves, CSF showed albuminocytological dissociation	Five cycles of plasmapharesis given Previously treated with doxycycline	Gradual improvement
Ju *et al*.[77]/2011	Serum O. tsutsugamushi titre + Serum O. tsutsugamushi titre +	NCS=demyelinating NCS=Acute sensorimotor polyneuropathy	IVIg+doxycycline Supportive	Improved Improved
Sakai *et al*.[78]/2016	IgM ELISA IgM ELISA	NCS=demyelinating NCS=axonal	IVIg IVIg	Improvement Improvement
Lee SH *et al*.[79]/2007	IgM ELISA	NCS=demyelinating	IVIg	Improved
Lee MS *et al*.[80]/2009	Indirect IFA Indirect IFA	NCS=demyelinating NCS=demyelinating	IVIg and prednisolone (5 days) IVIg and prednisolone (5 days)	Improved gradually Improved gradually
Miller Fisher syndrome				
Kim *et al*.[38]/2014	ELISA Anti-GQ1b antibodies negative	NCS=Reduced SNAPs, absent H reflexes	IVIg for 5 days (had previously received doxycycline)	Gradual recovery
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
Kalita *et al*.[83]/2015	Immuno-chromatographic assay of scrub typhus antibodies and/or a positive Weil-Felix test	CPK levels ranged between 287-3166 U/L EMG=short duration polyphasic potentials Muscle biopsy=evidence of vasculitis	Doxycycline	Complete clinical recovery and normalisation of CPK levels at one month
Young *et al*.[84]/2003	Indirect IFA	CPK=3250 U/L, deranged KFT; dark brown urine	Doxycycline	Complete recovery
Multi-axial involvement [Central plus Peripheral Nervous System]				
Kim *et al*.[85]/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*.[86]/2019	IgM ELISA	MRI=right frontoparietotemporal region, right thalamus, left temporal lobe, bilateral cerebellar hemispheres	Doxycycline	Improvement

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Table 2: Contd...

Author/Year	Diagnostic test for scrub typhus	Neuroimaging/other investigations	Treatment	Outcomes reported
Tandon *et al.*[87]/2019	IgM ELISA	C2-D1 cord hyperintensity, NCS: sensory motor axonal neuropathy	Doxycycline, albendazole, azithromycin and methyl prednisolone	Incomplete recovery
Phillips *et al.*[88]/2018	IgM) (solid-phase immunochromatographic assay	MRI brain and cervical spine: normal NCS=sensory motor demyelinating neuropathy; protein 146, cell count - 70 with lymphocytic predominance, sugar - 71 mg/dL	IVIg, doxycycline, rifampicin	Complete recovery

CPK=Creatine phosphokinase; CSF=cerebrospinal fluid; F=female; EMG=Electromyography; GBS=Guillain-Barre syndrome; IVIg=Intravenous immunoglobulins; IFA=Indirect immunofluorescence assay; M=male; MRI=magnetic resonance imaging; NCS=Nerve conduction studies; PCR=polymerase chain reaction

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.[29]

Encephalomyelitis

Two cases of acute encephalomyelitis have been reported in association with scrub typhus.[30,31] 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 at a tertiary centre in northern India had SE.[32] 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.[33]

Other central nervous system manifestations

Scrub typhus has been implicated as a cause of rapidly progressive cognitive impairment in one report.[34] 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.[35] However, the mechanism was unclear and the authors attributed it to a precipitous decline in blood pressure. Hence, strength of causation remains weak in both these reports.

Peripheral nervous system involvement in scrub typhus

Plexus involvement

Plexus involvement in the setting of scrub typhus is rare. We found three reports of plexus involvement with scrub typhus. Two of these reported brachial plexopathy which responded well to medical therapy.[36,37] One of these patients had presented with fever along with unilateral shoulder pain and shoulder weakness which resolved completely with doxycycline therapy [Table 2].

Radiculoneuropathy

We found 11 reports of acute radiculoneuropathy in association with scrub typhus.[38,73-80] 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.[38] Nearly all patients were managed with intravenous immunoglobulins. All patients showed improvement to complete resolution of weakness. The pathogenesis appears to be immune-mediated [Table 2].

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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Conflicts of interest
There are no conflicts of interest.

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