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Case Series

Internal Medicine Section

Rare Neurological Manifestations of Scrub Typhus: Case Series from a Tertiary Care Centre in Kerala, India

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ABSTRACT

Scrub Typhus has emerged as an important cause of acute febrile illness in various parts of India over the last decade. Scrub Typhus is caused by *Orientia tsutsugamushi*, a rickettsia transmitted through the bites of infected chigger larvae. The neurological manifestations of Scrub Typhus can be highly variable. The most common neurological manifestation is meningoencephalitis. In addition to two cases of meningoencephalitis, hereby, the authors report three different rare neurological manifestations of Scrub Typhus that presented in the second week of illness. These included isolated sixth cranial nerve palsy, opsoclonus myoclonus, and transient Parkinsonism. All the patients responded to treatment with doxycycline, and authors had to use steroids for one patient with opsoclonus myoclonus. A characteristic eschar was seen in only one patient out of the five cases. Therefore, a high index of suspicion for Scrub Typhus is needed in patients presenting with acute febrile illness and Central Nervous System (CNS) manifestations in endemic areas.

Keywords: Meningoencephalitis, Opsoclonus, Orientia tsutsugamushi, Parkinsonism

INTRODUCTION

Scrub Typhus is an infection caused by Orientia tsutsugamushi, a rickettsia. It is transmitted to humans by the bite of chiggers from trombiculid mites [1]. The bites of these chigger larvae form an eschar [1]. Scrub Typhus has clinical manifestations ranging from non specific febrile illness to severe multi-organ dysfunction [2]. The most common CNS involvement is meningoencephalitis [3]. Various other rare neurological manifestations include cranial nerve palsies, transverse myelitis, opsoclonus-myoclonus, acute disseminated encephalomyelitis, and Parkinsonism [4]. The disease is characterised by focal or disseminated vasculitis and perivasculitis, which may involve the liver, spleen, nervous system, lungs, and heart. The pathological findings in the CNS include mononuclear cell exudates in the leptomeninges and the presence of typhus nodules distributed throughout the brain substance [4]. Although various neurological manifestations are described in Scrub Typhus, original studies and case series published from present area are sparse.

Hereby, authors report five patients with rare neurological manifestations of Scrub Typhus who initially presented in the Emergency Department and were admitted to the Department of General Medicine at a tertiary care centre in South India.

CASE SERIES

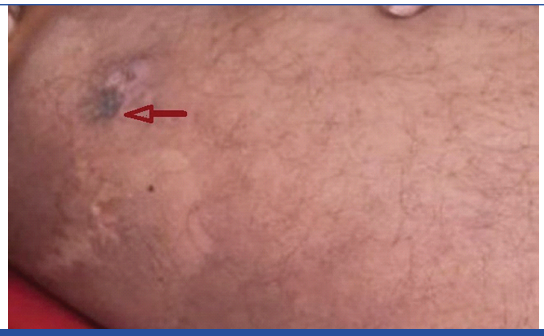
Case 1

A 66-year-old female, without any prior illness, was referred from a local hospital with intermittent fever for 15 days and double vision when looking to the left for four days. There was no history of seizures, altered sensorium, limb weakness, headache, vomiting, or pain on eye movement. Her neurological examination revealed left lateral rectus palsy [Table/Fig-1,2]. Pupils were equal, reactive to light, and accommodating. Her visual acuity, fundus examination, and other cranial nerve examinations were normal. The rest of the systemic examination was also normal. Blood investigations revealed mild thrombocytopenia (1.1 lac/mm^3), elevated Serum Glutamic Oxaloacetic Transaminase (SGOT) (109 IU/L), elevated Serum Glutamic Pyruvic Transaminase (SGPT) (91 IU/L), and normal bilirubin levels. Computed Tomography (CT) head and Magnetic Resonance Imaging (MRI) brain were normal. Lumbar puncture revealed mild lymphocytic pleocytosis (10 cells/microL) with normal protein (45 mg/dL) and normal glucose (50 mg/dL). Serological tests for leptospirosis, dengue, malaria, and hepatitis were negative, but the Immunoglobulin (Ig) M Enzyme-linked Immunosorbent Assay (ELISA) for Scrub Typhus was positive. She continued to have a fever for three days after admission. The patient was given intravenous doxycycline 100 mg for seven days. The fever gradually subsided after three days of treatment. Although her lateral rectus palsy persisted at discharge, it was completely resolved at the follow-up visit after three weeks. The most probable diagnosis of Scrub Typhus with isolated lateral rectus palsy was made, as the patient presented with fever and left lateral rectus palsy, positive scrub serology, and showed improvement with antibiotics.

[Table/Fig-1]: Clinical photograph of first patient showing left lateral rectus palsy on left gaze.
[Table/Fig-2]: Clinical photograph of first patient showing normal eye movement on right lateral gaze. (Images from left to right)

Case 2

A 42-year-old healthy male agricultural worker was admitted with fever, myalgia, and fatigue lasting for 15 days. He had no history of drug abuse, alcoholism, or medication intake prior to the illness. By the time he presented to us, he exhibited stiffness in all four limbs, which resulted in difficulty performing routine tasks with his hands. An eschar was noted on the left groin [Table/Fig-3]. He also had a mask-like face, tremors in both hands, and rigidity in all four limbs [Table/Fig-4]. Blood investigations revealed mild thrombocytopenia (platelet count 100,000/mm^3) along with elevated SGOT (98 IU/L) and SGPT (112 IU/L). A lumbar puncture revealed mild lymphocytic pleocytosis (15 cells/µL) with normal glucose (52 mg/dL) and protein (28 mg/dL). Imaging studies, including CT and Magnetic



[Table/Fig-3]: Eschar of case 2.

Resonance Imaging (MRI) of the brain, were normal. IgM Scrub Typhus serology was positive. This patient presented with fever, features of Parkinsonism, an eschar, and positive scrub serology, leading to a diagnosis of transient Parkinsonism associated with Scrub Typhus. He was treated with injection Doxycycline 100 mg twice daily for seven days, and his fever subsided after three days of treatment. After 10 days of admission, his muscle tone returned to normal, facial expressions improved, and tremors reduced without any conventional drugs for Parkinsonism. He was reviewed two weeks after discharge, and by that time, he had shown complete improvement, with normal facial expressions [Table/Fig-5]. This healthy male gradually developed rest tremors, rigidity, and a mask-like face suggestive of Parkinsonism during an acute febrile illness. The onset of Parkinsonism features occurred later in the illness and could be attributed to a delay in diagnosing Scrub Typhus.

[Table/Fig-4]: Showing mask like face (case 2). **[Table/Fig-5]:** Facial expression of the patient on review (case 2). (Images from left to right)

Case 3

A 38-year-old female presented to the Emergency Department with fever, headache, myalgia, and fatigue lasting for 10 days. The examination was unremarkable. Blood investigations revealed mild thrombocytopenia (67,000/mm^3) and transaminitis (SGOT 411 IU/L and SGPT 322 IU/L). The patient was started empirically on intravenous Ceftriaxone 1 gm twice daily and oral Doxycycline 100 mg twice daily. On the third day of admission, she developed involuntary jerky movements of the head associated with spontaneous rapid saccades present in all directions of gaze, without restriction of eye movement, suggestive of opsoclonus myoclonus syndrome. She developed head tremors and was unable to sustain herself in a sitting posture. An MRI scan of the brain was normal. Later, her IgM Scrub Typhus antibody test came back positive. A diagnosis of Scrub Typhus-associated opsoclonus myoclonus was made after ruling out other possible differential diagnosis, including autoimmune diseases, viral fevers, and paraneoplastic conditions, through suitable diagnostic tests. Her symptoms progressively worsened, and she was started on intravenous Methylprednisolone 1 gm for five days, following which she improved symptomatically. She was discharged after a week. Her eye movements had resolved completely, with mild persistence of head tremors, which also improved at the follow-up visit after two weeks.

Case 4

A 55-year-old male, without any co-morbidities, presented with a three-day history of fever and tiredness, along with altered sensorium for one day. Examination showed disorientation, neck stiffness, and no focal neurological deficits. Blood investigations revealed mild neutrophilic leukocytosis and thrombocytopenia (total count was 14,500 cells/mm^3 with 80% neutrophils; platelet count was 69,000/mm^3). Cerebrospinal Fluid (CSF) investigations were normal except for a borderline increase in protein of 98 mg/dL (as given in [Table/Fig-6]). IgM ELISA for Scrub Typhus was positive. He was diagnosed with Scrub Typhus with meningoencephalitis. The patient was treated with intravenous Doxycycline 100 mg twice daily for seven days. He improved progressively and was discharged after one week. He was asymptomatic at the follow-up visit after two weeks.

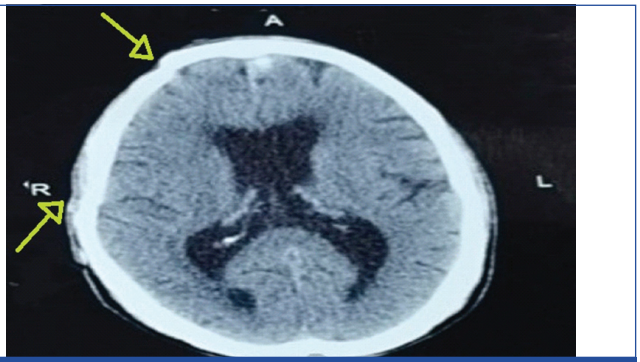
Parameters					
Clinical profile					
Age (years)/Gender	66/F	42/M	38/F	55/M	55 /M
Occupation	Farmer	Farmer	Housewife	Mason	Farmer
Past history	No	No No addictions, not on any medications	No	Old pulmonary TB	Previous History of ACOM* Aneursym Clipping Done 5 years back. Asymptomatic after surgery
Duration of fever	2 weeks	15 days	12 days	3 days	4 days
Neurological history	Double vision towards left side for 3 days	Stiffness of all 4 limbs tremor – 5 days	Abnormal movements head and eyes Tremor – 2 days	Altered sensorium	Altered sensorium
Level of consciousness	Normal	Normal	Normal	Disoriented and agitated	Disoriented and agitated
Skin lesion	-	Eschar left groin [Table/Fig-3]	-	-	_
CNS examination	Left lateral rectus palsy [Table/Fig-1,2]	Mask like facies, tremor on both hands, Rigidity all 4 limbs	Opsoclonus myoclonus tremor of head Ataxia	Neck stiffness	Neck stiffness
Investigations					
Haemoglobin (g/dL)	10.7	10.2	11.4	13.5	14.8
Total leucocyte count (cells/mm^3)	9900	9200	11900	14500	16000
Platelet (cells/mm^3)	1.1 Lac	1 Lac	67000	69000	61000
Random blood sugar (mg/dL)	123	134	115	240	97
SGOT/SGPT (IU/L)	109/91	98/112	411/322	181/72	157/152
Urea/ Creatinine (mg/dL)	36/1.3	28/1.1	75/0.8	60/1.2	158/1.8
Na/K (mEq/L)	138/4	135/4.5	138/4.4	126/4	132/4.5
Scrub IgM ELISA	Positive	Positive	Positive	Positive	Positive

Other investigations	ANA – Negative TSH – 3.4 Peripheral smear – no malarial parasite	ANA – Negative TSH – 2.3 S. Calcium -9.2 CPK – 45 Viral markers- Negative	ANA – Negative HIV, HBsAg, Anti HCV -Negative	IgM Dengue and Leptospirosis - negative	IgM Dengue and leptospirosis - negative
CSF - Total cells (cells/ microL)	10	15	0-1	35	20
CSF- differential count	All lymphocytes	All lymphocytes	All lymphocytes	All lymphocytes	All lymphocytes
CSF sugar (mg/dL)	50	52	51	190	60
CSF protein (mg/dL)	45	28	78	98	132
MRI brain	Normal	Normal	Normal	Normal	Not done due to aneurysm clipping
Diagnosis and course					
Neurological-diagnosis	Isolated sixth nerve palsy	Transient Parkinsonism	Opsoclonus Myoclonus	Meningoencephalitis	Meningoencephalitis
Outcome	Improved after a week, fully recovered after two weeks	Significant improvement on discharge	Significant improvement on discharge	Recovered	Recovered

[Table/Fig-6]: Summarised description of the patients.
Normal laboratory values: Haemoglobin 13-17 g/dL (men), 12-15 g/dL (women); Total leucocyte count : 4000-10,000 cells/mm^3; Platelets: 1.5-4.0 L cells/mm^3; RBS-<140 mg/dL; SGOT: 5-40 U/L; SGPT: 5-40 U/L; S. Creatinine: 0.8-1.3 mg/dL; Urea: 5-20 mg/dL; TSH -0.4-4 mIU/L; CPK-55-170 U/L male; Normal values of CSF-protein -15-45mg/dL; glucose-50-80 mg/dL; total cell count -<8 cell/microliters; CNS: Central nervous system; RBS: Random blood sugar; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; Na: Serum Sodium; K- Serum Potassium, HIV: Human immunodeficiency virus; HBsAg: Hepatitis B surface antigen; AntiHCV: Hepatitis C antibody; IgM- Immunoglobulin M; ANA: Antinuclear antibody; CPK: Creatine phosphokinase; TSH: Thyroid Stimulating hormone; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; *ACOM: Anterior Communicating Artery

Case 5

A 55-year-old male patient was admitted to the Medicine Department with fever for four days, altered sensorium, and headache for two days. The patient had a history of anterior communicating artery aneurysm five years prior, for which clipping was performed. He had been asymptomatic since, then. On examination, there was neck stiffness. His blood investigations revealed thrombocytopenia (platelet count 61,000/mm^3) with transaminitis (SGOT 157 IU/L, SGPT 152 IU/L). IgM Scrub ELISA was positive. A CT scan of the brain showed a calvarial defect in the right frontotemporal region due to the previous surgery [Table/Fig-7]. An MRI could not be performed due to the earlier clipping. His CSF study showed elevated protein (132 mg/dL) and normal sugar (60 mg/dL) with lymphocytic pleocytosis (20 cells/µL). In a patient with a history of fever, altered sensorium, neck stiffness, and positive scrub serology, a final diagnosis of Scrub Typhus with meningoencephalitis was made. He was treated with intravenous Ceftriaxone 1 gm and Doxycycline 100 mg twice daily for seven days. The fever subsided after three days, and his sensorium improved after five days of antibiotics. On follow-up after two weeks of discharge, he was asymptomatic.



[Table/Fig-7]: CT image showing Calvarial defect (case 5).

DISCUSSION

Scrub Typhus is caused by Orientia tsutsugamushi, a Gram-negative coccobacillus that belongs to the rickettsial class of infections. The bacillus is maintained through transovarian transmission in trombiculid mites, which serve as both the vector and the reservoir of infection. Humans are accidental hosts and become infected through the bite of chiggers (larval mites). Scrub Typhus is endemic and a re-emerging infection in eastern and southern Asia, northern Australia, and the islands of the western Pacific and Indian Oceans.

The chiggers are found in areas of heavy scrub vegetation, especially during the rainy season when mites lay eggs, in dense woods, rubber plantations, and crop fields. Several states in India have reported high numbers of cases of this disease: in the south, Tamil Nadu, Kerala, Andhra Pradesh, and Karnataka; in the north, Himachal Pradesh, Uttarakhand, Jammu and Kashmir; in the northeast, Meghalaya, Assam, and Nagaland; in the east, West Bengal and Bihar; and in the west, Maharashtra and Rajasthan [5]. In Kerala, the disease is common in rural areas among agricultural workers and residents of secondary vegetation, especially during the monsoon and post-monsoon periods. Thus, it is considered as a differential diagnosis of leptospirosis and dengue fever. The disease manifestations vary from mild febrile illness to severe fatal disease complicated by encephalitis, pneumonia, and myocarditis [6]. The classical neurological manifestation is meningoencephalitis, but literature reports cerebellitis, cranial nerve palsies, plexopathy, transverse myelitis, Guillain-Barré syndrome, opsoclonus, etc [6]. The lack of response to routine antibiotics like penicillins and cephalosporins usually raises suspicion of Scrub Typhus. Pathologically, it causes focal and disseminated vasculitis and perivasculitis in various organs, including the nervous system [6]. Immune-mediated mechanisms may contribute to perivascular mononuclear cell infiltration and vasculitis in Scrub Typhus patients [7]. The diagnosis is usually confirmed by IgM antibody detection by ELISA or by Polymerase Chain Reactions (PCR) tests [3].

In the first case, the patient developed left lateral rectus palsy after two weeks of fever, which responded to doxycycline treatment. All other causes of lateral rectus palsy, such as trauma, other infections, vascular ischaemia, malignancy, autoimmune diseases, and diabetes, were excluded. She was finally diagnosed with Scrub Typhus-associated abducent nerve palsy. Isolated cranial nerve involvement in Scrub Typhus is rare, and only a few cases have been reported in the literature [8]. The pathogenesis may involve micro-infarction of nerves due to Scrub Typhus-induced vasculitis [8]. Isolated as well as multiple cranial nerve involvement has been reported with Scrub Typhus.

In the second case, authors report transient Parkinsonism associated with Scrub Typhus. Various involuntary movements can occur as a result of nervous system infections. Transient Parkinsonism has been rarely reported as a neurological manifestation of Scrub Typhus [6]. It is recommended to consider infection-related Parkinsonism in patients with new-onset tremors, extrapyramidal signs, a mask-like face, and bradykinesia associated with fever An immune-mediated mechanism is thought to be the pathology behind transient

Parkinsonism [7]. The endothelial activation caused by *Orientia tsutsugamushi* can be associated with the release of large amounts of pro-inflammatory mediators, including Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-6, and IL-1β, which may lead to disruption of the blood-brain barrier, microglial activation, and damage to dopaminergic neurons [7].

In the third case, the patient developed opsoclonus myoclonus due to Scrub Typhus. Opsoclonus myoclonus is characterised by involuntary horizontal, torsional, and vertical eye saccades, along with involuntary jerky movements of muscle groups and ataxia [9]. Opsoclonus is a rare phenomenon in adults, occurring in patients as a paraneoplastic, autoimmune, para-infectious, or idiopathic phenomenon. Opsoclonus myoclonus in Scrub Typhus is exceedingly rare and usually manifests in the second week [10]. In cases of infection with O. tsutsugamushi, a significant IgM antibody titer is observed at the end of the first week, whereas IgG antibodies appear at the end of the second week. The pathogenesis is said to involve a rapid antibody class switch from IgM to IgG, which results in rising IgG titers. The present patient developed opsomyoclonus in the second week of her illness . She improved with steroids and doxycycline, suggesting an immune-mediated pathogenesis. As reported previously in other cases, opsomyoclonus in Scrub Typhus shows poor clinico-radiological correlation, and the MRI brain of our patient was also normal [11].

In the fourth and fifth cases, patients manifested meningoencephalitis. The most common neurological complication of Scrub Typhus is meningoencephalitis [6]. Meningoencephalitis due to Scrub Typhus responds very well to prompt early treatment. These two patients presented with neurological involvement in the first week of illness itself. The CSF findings in present cases showed mildly elevated protein and lymphocytosis [Table/Fig-6]. Patients improved with doxycycline and supportive measures.

Among the present case series, only one patient had an eschar. In a study conducted by Jamil MD et al., eschar was detected in 30.7% of patients with meningoencephalitis [12]. Identification of eschar may be difficult in individuals with Indian skin tone, as they can be hidden in the flexural areas, and the absence of an eschar cannot rule out Scrub Typhus. The time of onset of neurological manifestations varied; three patients experienced them in the second week of illness, which points towards immunological mechanisms. However, scrub meningoencephalitis can also be seen in the first week of illness, as the pathogenesis may be due to direct CNS invasion [13]. The diagnosis of Scrub Typhus is confirmed by the detection of Scrub Typhus IgM antibody in the serum by ELISA in all present cases. Leptospirosis and dengue fever are common febrile illnesses in Kerala, and both these and other possible causes were excluded by suitable laboratory tests.

Thrombocytopenia and transaminitis were observed in all patients [Table/Fig-6]. CSF studies showed mild lymphocytosis, mild protein elevation, and normal sugar levels in three out of five cases [Table/Fig-7].Similar CSF findings were detected in a study conducted by Sardana V and Shringi P from Rajasthan [2]. The lack of neutrophilic pleocytosis helps differentiate it from bacterial meningitis, but tuberculous meningitis remains a close differential diagnosis. Brain imaging was normal in all cases. Misra UK et al., reported abnormal MRI findings in only one out of 25 patients with neurological manifestations of Scrub Typhus [13].

All patients were treated with doxycycline as soon as the diagnosis was suspected. Methylprednisolone was administered to the patient with opsoclonus. All patients recovered completely within one to three weeks. Doxycycline can be added to the treatment regimen for febrile illnesses with CNS manifestations when Scrub Typhus is clinically suspected, especially in patients from endemic areas.

We searched for other studies showing Scrub Typhus with neurological manifestations, and the results are shown in [Table/Fig-8] [2,12-15].

Name of the author	Scrub typhus subjects	Findings
Sardana V and Shringi P [2]	5	2 meningoencephalitis 2 acute disseminated encephalomyelitis 1 cerebral venous sinus thrombosis
Misra UK et al., [13]	37	13 meningoencephalitis 6 encephalitis 9 encephalopathy
Saxena P et al., [14]	7	3 meningoencephalitis 1 intracerebral bleed 1cerebral venous thrombosis 1 cerebellitis 1 GBS
Ghosh R et al., [15]	50 cases with neurological manifestations	10 rare manifestations (PRES, Opalski syndrome, parkinsonism, cerebellitis, isolated opsoclonus, transverse myelitis, polyradiculoneuropathy, myositis, transient behaviour change, fibromyalgia)
Jamil MD et al., [12]	113 total Scrub Typhus patients	15 meningoencephalitis

[Table/Fig-8]: Comparison of other studies showing neurological manifestation of Scrub typhus [2,12-15].
PRES: Post reversible encephalopathy syndrome

CONCLUSION(S)

The present case series highlights the various rare neurological manifestations of Scrub Typhus. In cases of short febrile illness with neurological manifestations, Scrub Typhus should be considered as one of the differential diagnoses, even in the absence of eschar and unremarkable neuroimaging, especially in endemic areas. Although immunological mechanisms are postulated in the neurological manifestations of Scrub Typhus, there was a remarkable response to doxycycline in most of present cases (except in case number 3), emphasising the importance of early diagnosis and prompt treatment, resulting in favorable outcomes.

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