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Profile of Neurological Manifestations of Scrub Typhus in a Rural Tertiary Care Hospital

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ABSTRACT

Scrub typhus is a rickettsial infection caused by Orientia tsutsugamushi. Scrub typhus is an important cause of acute febrile illness in India. Central nervous system (CNS) involvement is a known complication of scrub typhus, which ranges from aseptic meningitis to frank meningoencephalitis. Based on this aim of our study is to estimate the incidence and describe the pattern of neurological involvement among patients with scrub typhus in a rural tertiary care hospital. This study was done as a Prospective observational study at Critical care unit and medical wards of Government Dharmapuri Medical College and Hospital for a period of 1 year from August 2021 to July 2022 in 50 patients diagnosed with scrub typhus with neurological manifestations Clinical examination, blood samples for routine blood investigations, fever profile, Neuro imaging-CT or MRI, CSF examination was done in all patients. All patients in our study presented with fever and myalgia, among neurological presenting complaints in particular. Headache was most common seen in 84% of patients followed by altered sensorium in 72% of patients. On further evaluation with radiological and clinical manifestation, following were the clinical manifestation with Nearly 64% had meningitis and meningoencephalitis, Cerebellitis and encephalopathy was seen in 8%, Unusual cases of transverse myelitis, Acute demyelinating encephalomyelitis were also seen. In our study, CSF examination was done in 33 patients with altered sensorium. Increased lymphocytes was seen in 14 patients, increased protein (>45mg/dl) in 17 cases. Low sugar (<20mg/dl) seen in 9 cases. Neurological manifestations are very common in scrub typhus. Rickettsial disease can present with various neurological features of varying severity. Knowledge of these manifestations will enable clinicians to consider scrub typhus as one of the differential diagnoses of acute febrile illness with neurological involvement. The neurological complications in scrub typhus have good prognosis if diagnosed and treated early.

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Key Words
Scrub typhus, CNS, manifestation, meningoencephalitis

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INTRODUCTION

Scrub typhus is a rickettsial infection caused by Orientia tsutsugamushi, which is a Gram negative obligate intracellular coccobacillus that is transmitted to the humans by the bite of larval stage (chigger) of trombiculid mite. The bites of these chiggers leave the characteristic "eschar," which is pathognomonic of scrub typhus[1,2]. The characteristic eschar is seen in 40-50% of patients and may be inconspicuous as it is often present in areas like groin, gluteal folds, breast folds and external genitalia and may go unnoticed in dark skinned people[3]. The disease has been reported from all over the world, but it is endemic in terrains of the tsutsugamushi triangle, a geographical region comprising South and East Asia and the Southwest Pacific[4]. In India, studies have shown the endemic nature of scrub typhus in many states and union territories. Scrub typhus is an important cause of acute febrile illness in India[4]. Case fatality rate may be as high as 30% if left untreated[5]. Infection manifests clinically as a nonspecific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhea and breathlessness and ranges to severe multi organ dysfunction[6]. Central nervous system (CNS) involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis[7]. Various neurological manifestations include meningoencephalitis, meningitis, encephalitis, encephalopathy, seizure, myelitis, ADEM, cranial neuropathies like sixth, seventh, mononeuritis multiplex, brachial plexopathy, Guillain-Barre syndrome and rarely stroke. The most common reported manifestation is meningoencephalitis[8,9]. The pathological findings in CNS in scrub typhus include diffuse or focal mononuclear cell exudates in leptomeninges and presence of typhus nodules (cluster of microglial cells) that are distributed throughout brain substance[9]. A large study showed that CNS was involved at least slightly in almost all patients suffering from scrub typhus, however, focal neurological deficit occurred rarely[10]. Meningitis/meningoencephalitis have been reported in 14-83% of patients with scrub typhus. In a study by Rana *et al.,* 37 patients with symptoms and/or signs suggestive of neurological dysfunction were included in the study. Of these, 31 (84%) patients had altered sensorium, 15 (40%) had meningoencephalitis, 3 (8%) had seizures[8]. The involvement of 2nd, 3rd, 6th, 7th and 8th cranial nerves has been documented in patients with scrub typhus. The presence of unilateral or bilateral deafness may occur in many rickettsial diseases and mechanism for hearing loss has been assumed vasculitis induced cochlear damage., however, it could be immune mediated also. The presence of hearing loss concurrent with fever is reported by as many as one-third of patients with scrub typhus and is a useful diagnostic clue to scrub typhus in endemic areas[11]. A study by Rana *et al.* reported cerebellitis in 11% cases of scrub typhus with neurological involvement. Cerebellitis occurred in isolation and in association with generalized neurological involvement also[8]. Lee *et al.* described Guillain-Barré syndrome (GBS) associated with scrub typhus. The diagnosed of GBS was based on neurological examination and electromyography. O. tsutsugamushi antibody or antigens presented on infected cells are suspected to activate mimicry on myelin cells or peripheral nerve axons, which elicits immune reactions similar to autoimmune diseases[12]. Based on this aim of our study is to estimate the incidence and describe the pattern of neurological involvement among patients with scrub typhus in a rural tertiary care hospital.

MATERIALS AND METHODS

This study was done as a Prospective observational study at Critical care unit and medical wards of Government Dharmapuri Medical College and Hospital for a period of 1 year from August 2021 to July 2022 in 50 patients diagnosed with scrub typhus with neurological manifestations Clinical examination, blood samples for routine blood investigations, fever profile, Neuro imaging-CT or MRI, CSF examination was done in all patients. Patients with age >18 years with Positive IgM antibody to scrub typhus by ELISA or presence of ESCHAR or both with signs and symptoms suggestive of neurological involvement were included. While patients not hospitalized were excluded.

RESULTS AND DISCUSSIONS

In our study of 50 patients, 26 patients were male and rest 24 patients were female in a ratio of 1.08: 1. The age range of patients in our study was 21-72 years with mean age of 58.72 years. Most of the patients were from rural population. All patients in our study presented with fever was present in all cases followed by myalgia in 47 cases, nausea/vomiting was present in 36 patients. Jaundice was present in 34 patients. Respiratory symptoms was present in 22 patients and abdominal pain was present in 20 patients. Lymphadenopathy was seen in 13 patients and hepatomegaly in 18 patients. More importantly eschar was present in 30(60%) of patients. Among neurological presenting complaints in particular. Headache was most common seen in 82 % of patient's, altered sensorium in 72% of patients. Other presenting complaints was seizure, ataxia and weakness in few cases.

Table 1: Presenting Neurological Complaints

Presenting Complaints	No. of Patients	Percentage
Altered Sensorium	36	72%
Headache	41	82%
Seizure	8	16%
Ataxia	4	8%
LL Weakness	3	6%
Hemiparesis	5	10%
Myoclonus	1	2%
Double Vision	1	2%

On further evaluation with radiological and clinical manifestation, following were the clinical manifestation with Nearly (32) 64% had meningitis and meningoencephalitis, Cerebellitis was seen in (4) 8%, encephalopathy was seen in (4) 8%, Unusual cases of Acute transverse myelitis-(1) 2%, Acute demyelinating encephalomyelitis-(1) 2% cranial nerve palsy, cerebral infarct was seen in 2 patients each. GBS, CVT and cerebral hemorrhage was also seen.

Table 2: Neurological Manifestations

Neurological Involvement	No of Patients	Percentage
Meningoencephalitis	26	52%
Meningitis	6	12%
Transverse Myelitis	1	2%
Encephalopathy	4	8%
Neuromyelitis Optica	1	2%
ADEM	1	2%
GBS	1	2%
Cerebellitis	4	8%
Cerebral Hemorrhage	1	2%
Cerebral Infarct	2	4%
CVT	1	2%
Cranial Nerve Palsy	2	4%

Lab investigation was done in all patients, anemia was present in 26 (52%) of patients. Leucocytosis was present in 28 (56%) patients, thrombocytopenia in 48(96%) of patients. Renal function test was deranged in 29(587%) patients and liver function test was deranged in 46 patients. IgM scrub was positive in 46 patients. In our study, CSF examination was done in 33 patients with altered sensorium. Increased lymphocytes was seen in 14 patients, increased protein (>45mg/dl) in 17 cases. Low sugar (<20mg/dl) seen in 9 cases. CT was normal in 18 patients. Neuroimaging abnormalities noted were meningeal enhancement, abnormal hyper intense signals in grey matter on T2 and FLAIR and cerebral infarct. 6 patients had neurological manifestations but did not have altered sensorium. Finally in our study group 47 patients improved with anti-rickettsial therapy and 3 patients died.

Scrub typhus was endemic in India in the past decade especially in Himachal, UP and some states of south India, but since the past few years scrub typhus is emerging as a life-threatening illness in other parts of India. Previous studies that were published reported cases of scrub typhus and their outcome from states like Himachal Pradesh, Uttar Pradesh and Pondicherry., this is the first case series reported from Dharmapuri district with extensive work up and showing importance of early diagnosis and treatment. Nervous system involvement is a common complication of scrub typhus infection. Orientia tsutsugamushi enters the CNS by invasion of endothelial cells in blood vessels. cytokine released by acutely inflamed vascular endothelial cells secondary to invasion in blood vessels damage endothelial integrity causing fluid leakage. There is localized platelet aggregation, polymorph and monocyte proliferation, leading to ingots[13,1]. CNS involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis[14]. Many studies in India and in other countries found that meningoencephalitis is a most common neurological complication of scrub typhus. A study done by Rana *et al.* found that the most common neurological manifestation was meningoencephalitis (40%)[1]. A cross-sectional study on 37 patients published by Mishra *et al.* found two-thirds of patients with scrub typhus had neurological involvement manifesting as meningoencephalitis, encephalitis, or encephalopathy[13], but cerebrospinal fluid findings can mimic tuberculous meningitis and viral meningoencephalitis[14]. In our study, 52% of patients had meningoencephalitis. Scrub typhus as a cause of ADEM is extremely rare, pathophysiology is obscure, but it has been postulated to result from an autoimmune response to myelin basic protein triggered by infection as in our cases it may be due to cross reactivity of IgM antibodies to myelin protein[8]. One case in our study had ADEM. Most reports of meningitis are from Korea, India and Taiwan. Meningeal signs were seen in 14% of patients with scrub typhus in a study conducted in Assam and Burma way back in 1946[15]. In a study by Pai *et al.,* on 25 patients with CNS involvement, only half of them had CSF lymphocytosis and only a third had elevated protein[7] In our study, CSF examination was done in 33 patients with altered sensorium. Increased lymphocytes was seen in 14 patients, increased protein (>45mg/dl) in 17 cases. Low sugar (<20mg/dl) seen in 9 cases.

CONCLUSION

Neurological manifestations are very common in scrub typhus. Rickettsial disease can present with various neurological features of varying severity. Knowledge of these manifestations will enable clinicians to consider scrub typhus as one of the differential diagnoses of acute febrile illness with neurological involvement. The neurological complications in scrub typhus have good prognosis if diagnosed and treated early.

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