Original Article

Tsutsugamushi Disease (Scrub Typhus) Meningoencephalitis in North Eastern India: A Prospective Study

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Abstract

Background: Scrub typhus is rampant in northern, eastern, and southern India. Central nervous system involvement in the form of meningitis or meningoencephalitis is common in scrub typhus. As specific laboratory methods remain inadequate or inaccessible in developing countries, prompt diagnosis is often difficult. **Aim:** The aim of this study was to characterize neurological complications in scrub typhus from northeastern region of India. **Subjects and Methods:** We did a prospective study of scrub meningoencephalitis at North Eastern Indira Gandhi Regional Institute of Medical Sciences among patients admitted to hospital between October 2009 and November 2011. The diagnosis was made based on the clinical pictures, presence of an eschar, and a positive Weil–Felix test (WFT) with a titer of >1:160 and if required a positive scrub IgM enzyme-linked immunosorbent assay. Lumbar puncture was performed in patients with headache, nuchal rigidity, altered sensorium or cranial nerve deficits, and magnetic resonance imaging (MRI) brain performed if needed. **Results:** Twenty-three patients of scrub typhus meningitis that were serologically confirmed were included in the study. There were 13 males and 10 females. Fever ≥1 week was the most common manifestation (39.1%).Interestingly, none had an eschar. Median cerebrospinal fluid (CSF) cell count, lymphocyte percentage, CSF protein, CSF glucose/blood glucose, CSF ADA were 17 cells/μL, 90%, 86 mg/dL, 0.6605 and 3.6 U/mL, respectively. All patients were treated with doxycycline. There was no mortality in our study. **Conclusions:** Absence of Eschar does not rule out scrub typhus. Clinical features and CSF findings can mimic tuberculous meningitis so misdiagnosis may lead to unwarranted prolonged empirical antituberculous therapy in cases of lymphocytic meningoencephalitis. Delay in treatment can be potentially fatal. WFT still serves as a useful and affordable diagnostic tool for this disease in resource-poor countries.

Key words: Eschar, Meningoencephalitis, *Orientia tsutsugamushi*, Scrub Typhus, Weil–Felix Test

Introduction

Scrub typhus is a zoonosis caused by *Orientia tsutsugamushi* and is one of the most common infectious diseases of rural southern Asia and South-eastern Asia, and the western Pacific.[1] Scrub typhus is one of the most covert re-emerging infections of the present time. The magnitude of this problem continues to be underestimated in many endemic areas, especially in India where scrub typhus is fast becoming an important cause of acute meningitis.[2] The disease is transmitted to humans by the bite of the larvae Leptotrombidium mite (chigger).[3] The disease often appears as a nonspecific febrile illness. The clinical pictures of scrub typhus are typically associated with fever, rash, myalgia, and diffuse lymphadenopathy.[4] The pathognomonic clinical sign of scrub typhus is an "eschar" (40–50%) which may be inconspicuous as it is often present in areas like the groin, gluteal cleft, inframammary region, and the external genitalia and may also go unnoticed in dark-skinned people.[5] Furthermore, the patients are usually unaware of the bite, as the eschar is painless and does not itch. The mite has four life cycle stages: Egg, larva,

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nymph, and adult. However, scrub typhus meningoencephalitis is thought to be an unclear entity.[2] Tsutsugamushi induces vasculitis leading to symptoms of systemic organ invasion including meningitis and meningoencephalitis.[6] CSF studies are similar to that of tuberculous meningitis (TBM) and viral etiologies.[7] Due to inadequate or inaccessible laboratory tests in developing countries delay in the diagnosis of scrub typhus meningitis and encephalitis is associated with higher mortality.[2] It has been reported from various regions of the Indian subcontinent, however, there is no such report of cases from northeastern region of India.[8,9] Meghalaya is a state in northeast India with a predominantly rural tribal population. It is a plateau with a highest altitude of 1,961 m above sea level. In the coming years, scrub typhus meningitis may become a major public health problem in North East India and also highlights the diagnostic challenges faced in a resource-limited setting along with peculiar observations. This has never been reported to the best of the authors' knowledge and belief.

Subjects and Methods

By consecutively sampling, between October 2009 and November 2011, we conducted a prospective study in patients suffering with scrub typhus meningoencephalitis under the auspices of the neurology department of a tertiary care teaching institution, an autonomous institute under the Ministry of Health and Family Welfare, Government of India. It is the apex referral center for the state of Meghalaya located in North East India. Patients above 18 years of age who exhibited altered mental states such as confusion, obtundation, stupor or coma without evident cause such as shock or hypoglycemia or presence of both headache and neck stiffness, or cerebrospinal fluid (CSF) counts of >5 leucocytes/mm^3 were considered for inclusion in the study. The diagnosis of scrub typhus was made by a positive Weil–Felix test (WFT) and but was not confirmed by a serum IgM enzyme-linked immunosorbent assay (ELISA) due to inaccessibility. Among the confirmed scrub typhus cases, lumbar puncture was performed in patients with clinical features suggestive of meningitis. In addition to cell counts, CSF protein, and glucose estimation, the centrifuged deposit was subjected to the Grams, Ziehl-Neilsen, and India ink staining techniques to identify bacteria, acid-fast bacilli, and Cryptococcus, respectively. Patients who had a positive WFT and on CSF analysis suggesting meningitis, in whom other causative organisms were not found on stains or cultures, were defined as scrub meningitis cases. At presentation, a thorough history, physical examination, and laboratory tests were performed on patients who were enrolled in this study. Signed informed consent was obtained from each patient prior to inclusion in the study. This study was approved by the institutional Ethics commetee of our hospital.

Result

During the study period, 23 patients fulfilled the criteria for meningitis or meningoencephalitis caused by *O. tsutsugamushi*. Thirteen of these cases were male, and 10 were female [Table 1]. The majority of patients were either farmers or housewives (84%). Ages ranged from 19 to 68 years. The most frequent presenting complaints were fever (100%), headache (91.3%), nausea and vomiting (73.9%), altered sensorium and seizures. Cases of scrub typhus that presented with altered sensorium were 14 (60.8%). Signs of raised intracranial pressure in the form of bilateral papilledema and radiological features of cerebral edema on noncontract computed tomography (CT) scan of the brain were found in 4 cases. One case had cortical blindness and magnetic resonance imaging (MRI) brain of that patient revealed bilateral occipital infarcts. Focal neurological findings were noted in two patients who developed the hemiparesis. MRI of the brain in these cases showed internal capsule infarcts. No other underlying causative risk factors for the infarct could be determined on clinical and laboratory evaluation. Nonspecific lung infiltrates with predilection for the middle zone was observed in two cases. The pathognomonic eschar was not seen in any patient. Among the laboratory parameters the laboratory parameters, leukocytosis was observed in 13 patients (56.5%), thrombocytopenia 14 patients (60.8%), raised transaminases ALT/AST >60IU in 15 patients (65%) [Table 2]. Median cerebrospinal fluid (CSF) cell count, lymphocyte percentage, CSF protein, CSF glucose/blood glucose, CSF ADA were 17 cells/μL, 90%, 86 mg/dL, 0.6605 and 3.6 U/mL, respectively [Table 3]. All CSF samples were negative for Gram-stain, India ink, culture, acid-fast bacilli. Blood cultures were sterile. WFT was done in all the cases and showed OX K titer >1:160 in 21 cases and 2 cases had >1:320. All patients with meningitis were treated with doxycycline (100 mg BD for 14 days). Patients were additionally administered dexamethasone and Mannitol if they had altered sensorium or cranial nerve deficits. None of our patients

Table 1: Clinical features of patients included in the study

Symptoms	Number of patients (%)
Fever	
≤7 days	9
7-10 days	7
≥2 weeks	7
Myalgia	19 (82.6)
Jaundice	6 (26.0)
Breathlessness	7 (30.4)
Cough	8 (34.7)
Headache	21 (91.3)
Nausea/vomiting	17 (73.9)
Seizures	6 (26.0)
Clinical signs	
Altered sensorium	14 (60.8)
Pedal edema	10 (43.4)
Hypotension/shock	5 (21.7)
GCS	11±4.0
Icterus	6 (26.0)
Lymphadenopathy	3 (13)
Splenomegaly	6 (26.0)

GCS: Gianotti-crosti syndrome

received antiviral or antitubercular therapy. Doxycycline has better central nervous system (CNS) penetration than tetracycline and does not cross the blood-brain barrier beyond 15–30%. *O. tsutsugamushi* has been shown to have developed antibiotic resistance in northern Thailand to chloramphenicol and tetracycline. Doxycycline remains the drug of choice. As none of our patient was pregnant, no one received Azithromycin All patients responded to the initial antibiotic therapy, and no case of clinical drug resistance was found. The average period of defervescence was 2.8 days, and no death was reported. Focal neurological deficits improved gradually in patients with infarcts but repeat MRI Brain could not be performed due to costs.

Table 2: Laboratory investigation and results of patients

Laboratory parameters	Number of patients (*n*=23) (%)
Raised alkaline PO4 (>120 IU/L)	14 (60.8)
Raised serum creatinine (>1.0 mg %)	7 (30.4)
Raised bilirubin (>1.2 mg %)	6 (26.0)
Leukocytosis (>11000/µl)	13 (56.5)
Thrombocytopenia (<10×10^6/µl)	14 (60.8)
ALT (>40 IU/L)	9 (39.1)
AST (>40 IU/L)	6 (26.0)
CXR abnormalities	3 (13)
WFT >1:160	23 (100)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WFT: Weil-Felix test, CXR: Chest X-ray

Discussion

This paper presented the clinical profiles of patients with scrub typhus meningoencephalitis from north east India**.** A recent publication of scrub typhus meningitis from South India reported meningitis as a common CNS complication.[7] However, cases from northeast India have not been reported to the best of authors' knowledge and belief. Scrub typhus cases are prevalent in most part of the world but are generally incapacitating and notoriously difficult to diagnose.[10] Untreated cases can have a fatality as high as 30–35% but when diagnosed correctly they are easy and simple to treat.[11] The clinical and laboratory features of scrub typhus are nonspecific. Full blown scrub typhus cases were seen in the preantibiotic era. With early usage of antibiotics, all features of the disease are not likely to be encountered. Hence, it is necessary to maintain a high index of clinical suspicion. The purpose of this study was to characterize scrub typhus meningitis and meningoencephalitis in an endemic area like ours. Previous studies from various authors reveal that in India the eschar is generally not commonly seen and so was it in our study.[12] The painless chigger bite can occur in any part the body, but it is located in areas that are hard to examine such as the genital region or under the axilla.[5] The reported percentages of eschar formation showed substantial variations across studies and ranged from 5% to 100%.[12] However, it is relatively difficult to visualize on dark skinned individuals as in Indians. Scrub typhus affects both the central and peripheral

Table 3: Clinical manifestations and CSF picture of patients with scrub typhus meningoencephalitis

Patient	Age, gender	Neurological deficits	Cells (cells/µL)	Lym (%)	Prot (mg/dl)	Glu (mg/dl)	CBS	ADA (U/mL)	WFT
1	50, female	Altered sensorium, irrelevant talking, normal CT brain	187	97	268	98	124	6.8	1:160
2	23, female	Seizures, MRI brain normal	7	90	90	140	96	1.8	1:160
3	35, male	Hemiparesis, MRI brain internal capsular infarct	8	80	45	56	96	2.4	1:160
4	44, female	Bilateral 6th CNP, normal CT brain	260	90	86	82	107	5.8	1:160
5	45, female	Loss of consciousness, normal CT brain	156	94	380	67	108	7.2	1:320
6	27, female	Seizures, MRI brain normal	13	80	35	56	71	3	1:160
7	19, male	Cortical blindness, MRI brain occipital infarct	10	70	34	49	108	1.7	1:160
8	29, male	Nausea/vomiting, headache, neck stiffness CT brain	6	90	210	78	95	4.2	1:320
9	27, female	Drowsiness, power 4/5, MRI brain normal	156	95	180	100	148	5	1:160
10	23, male	Bilateral, CNP, papilledema, CT brain edema	368	90	1060	76	148	5.6	1:160
11	48, male	Seizures, MRI brain normal	24	78	58	70	105	4.6	1:160
12	55, male	Altered sensorium, abusive language, normal CT brain	79	90	400	62	90	2.4	1:160
13	67, female	Agitated, neck stiffness, normal CT brain	13	90	78	68	130	1.6	1:160
14	53, female	Hemiparesis, MRI brain internal capsular infarct	7	100	45	58	88	2.6	1:160
15	31, male	Seizures, MRI brain normal	16	90	56	68	120	3.7	1:160
16	68, male	Drowsiness, MRI brain normal	23	86	39	37	140	0.9	1:160
17	37, male	Seizures, Todd's palsy, MRI brain normal	6	100	68	58	98	1.3	1:160
18	44, female	Unconscious, MRI brain normal	17	80	94	74	130	6.4	1:160
19	45, male	Bilateral 6th CNP, normal MRI brain	15	90	86	64	256	2.1	1:160
20	34, male	Seizures, MRI brain normal	9	100	42	72	105	3.1	1:160
21	36, male	Altered sensorium, normal CT brain	187	86	350	72	109	8.4	1:160
22	26, male	Agitated, neck rigidity	357	80	160	120	96	3.6	1:320
23	43, female	Bilateral 6th CNP, bilateral nystagmus, normal MRI brain	196	96	78	84	98	3.8	1:160

CT: Computed tomography, CNP: Cranial nerve palsy, MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, Lym: Lymphocyte percentage, Cells: Normal range (0-5 cells/µL), Prot: CSF protein (normal range 20-40 mg/dl), Glu: CSF glucose (normal range 40-70 mg/dl), CBS: Corresponding blood sugar (normal range <140 mg/dl); ADA: Adenosine deaminase (<10 U/mL), WFT: Weil-Felix test (≥1:160 as positive)

nervous system.[7] Tsutsugamushi is the rickettsia with the meningeal involvement. CNS complication is widespread and includes the infarction, cerebellitis, hemorrhage, encephalitis demyelination, subdural hematoma, and meningitis. These may manifest as altered sensorium, restlessness, motor weakness, seizures, meningism, and cranial nerve deficits.[7] The rickettsia directly invades the CSF. A prospective study of Thai children revealed that scrub typhus was the second most common cause of aseptic meningitis next to Japanese encephalitis.[13] None of our patients had a repeat CSF study due to serological diagnosis and clinical recovery within 72 h.

Weil–Felix test (OX-K) was considered positive with the titers of 1:160 or more in the present study based on manufactures' guidelines and cut off used in some other studies elsewhere.[14] Furthermore, there are no epidemiological studies done from this region for establishing such cut-offs. Other studies from India have taken a cut off of as low as 1:80 as positive while still others have demonstrated that a cut off >1:320 indicates a definitive diagnosis of scrub typhus.[11] Most of western literature have advised against performing this test for diagnosis of rickettsial infection.[15] The poor sensitivity is now well demonstrated, but indirect immunofluorescence antibody assay and indirect immunoperoxidase require highly trained personnel and production of antigens may vary among different laboratories, leading to inconsistencies in the interpretation of results.[16] WFT can be used as a screening test. It helps to detect more cases than misdiagnosed ones and when positive is reasonably specific. In spite of all these drawbacks, WFT still serves as a useful and affordable diagnostic tool for laboratory diagnosis of rickettsial diseases in resource-poor countries. Isaac *et al*.[17] have demonstrated that the sensitivity of WF test was 30% at the breakpoint titer of 1:80, but the specificity and positive predictive value were 100%. Evaluations done in different laboratories have showed that this test had a specificity of over 98% and a sensitivity of about 43%.[18] In several areas around, the world, WF test has proved useful in documenting the presence of these infections for the first time[19] Hence, WF test is still not entirely obsolete in resource-limited parts of the world and has to be interpreted in the correct clinical context.[20] as done in the present study. Primary infection produces a rapid rise in IgM antibodies within 8 days, whereas secondary or reinfection is characterized by a sharp rise in IgG levels, with a variable IgM response. Since ICT also detects IgG antibodies, the patient may have had a secondary infection and thus the positive result. It has been suggested that recombinant antigen-based ELISA is suitable in moderately equipped laboratories in the scrub typhus endemic regions.

Subacute onset of meningitis like TBM is also considered an additional diagnostic challenge. Both TBM and scrub typhus meningitis showed picture of lymphocyte-predominant CSF. Adenosine deaminase (ADA) >10 increases the probability of TBM.[21] on the contrary, slightly decreased CSF glucose and presence of focal signs in TBM may help in differentiating it from scrub typhus meningitis.[2] In addition, the elevated transaminases tend toward scrub typhus infections, which would be not so usual in TBM unless they were already on treatment.[2] CSF Adenosine deaminase (ADA) levels for our patients were less than 10 U. Hence, ADA levels may be helpful in differentiating scrub meningitis from TBM but more studies are necessary to confirm. Rifampicin is alternatively used to treat severe scrub typhus. Presence of lymphocytic CSF in a given patient, with improvement following antituberculous therapy (ATT), may mask the diagnosis of scrub typhus.[7] Recovery in meningoencephalitis is fast with appropriate therapy. All neurological abnormalities in our study recovered within 3–7 days of doxycycline therapy. Doxycycline remains the drug of choice. All patients responded well. There was no death due to meningitis which can be explained by the fact that the authors had high index of suspicion as this was a prospective study. Accordingly, necessary investigations were sent at the earliest leading to early diagnosis followed by institution of appropriate therapy. The major limitation of this study is small sample size of the study and the inability to do a confirmatory test in all cases due to nonavailability of the test in our Institute and the high cost of performing the same from private laboratories.

Conclusions

Scrub typhus is a re-emerging cause of acute and subacute meningitis, which can be difficult to diagnose. The eschar, a path gnomonic clinical feature, is often not present, and as the larval bite is painless, a history of insect bite is unlikely to be solicited from the patients. Due to the presence of lymphocytic pleocytosis with increased CSF protein; TBM is a close differential diagnosis. Hence, misdiagnosis may lead to unwarranted prolonged empirical antituberculous therapy in cases of lymphocytic meningoencephalitis. Diagnosis of scrub typhus meningitis is important as it is treatable with inexpensive antibiotics and if left untreated, can be potentially fatal. The highlight of this study is that it is the first, prospective study of scrub meningitis from northeastern region of India. What is noteworthy in this study that the WFT can still be fruitful for diagnosing this disease in a resource-limited setup? Our study, however, is limited by its size, and further research, on a larger scale, is warranted for this potentially fatal disease.

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