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Original Research Article

A study of scrub meningoencephalitis and keeping it as a common differential diagnosis

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ABSTRACT

Background: Scrub typhus is caused by the organism *Orientia tsutsugamushi*, transmitted by trombiculid mites. Meningoencephalitis as a cause of mortality in cases of scrub typhus is becoming a common entity now. Aims and objectives were to study the incidence of meningoencephalitis in scrub typhus cases admitted to our hospital and stress the importance of keeping it as a common differential diagnosis.
Methods: A descriptive observational study of 39 diagnosed cases of scrub typhus admitted to our hospital for 6 months duration (May 2018 to October 2018) was conducted. Data concerning the cases were recorded and analyzed using appropriate statistics.
Results: Out of 39 cases admitted, 8 patients were diagnosed as having meningoencephalitis. Patients with meningoencephalitis had severe thrombocytopenia when compared to those without any central nervous system (CNS) symptoms. All patients responded well to doxycycline therapy with no mortality amongst cases under study.
Conclusions: There have been numerous outbreaks of scrub typhus in our state of Rajasthan, especially in the Hadoti region. And in recent years, scrub typhus has been an important contributor to the newer class of emerging infections causing mortality in India. Meningoencephalitis although rare forms a major part of the complications of scrub typhus.

Keywords: Acute febrile illness, Scrub typhus, Meningoencephalitis

INTRODUCTION

Scrub typhus is also known as tsutsugamushi disease is an acute febrile illness caused by *O. tsutsugamushi*. It is a mite-born disease characterized by fever with a headache, suffused face, lymphadenopathy, eschar, multi-organ involvement and rapid response to doxycycline. Scrub typhus is seen in all terrains of the tsutsughamushitriangle which extends from Pakistan, India and Nepal in the West, to South-Eastern Siberia, Japan, China and Korea in the North to Indonesia, the Philippines, Northern Australia and the Pacific Islands in the South and is related mostly to agricultural and outdoor activities.[1,2] Rickettsiae are small gram-negative obligate intracellular bacilli transmitted by arthropod vectors. They infect vascular endothelium and reticuloendothelial system. The family consists of the following genera: *Rickettsia*, *Orientia*, *Ehrlichia*, *Anaplasma*, *Neorickettsia*, *Candidatus neoehrlichia* and *Coxiella* genus rickettsia consists of the typhus fever group, the spotted fever group and scrub typhus.

CNS involvement is a known complication of scrub typhus which ranges from meningitis to frank meningoencephalitis.[3,4] Neurological complications include seizure, cranial nerve deficits, vasculitic cerebral infarct, brain hemorrhages, polyneuropathy, sensorineural hearing loss, meningitis or meningoencephalitis.[3,5-7] These manifestations may be due to direct invasion of CNS by the organism as has been shown by polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) or maybe due to the unique propensity of the organism to infect vascular

endothelial cells, thereby causing microinfarct.[7,8] Scrub typhus meningitis/meningoencephalitis diagnosis based on clinical features, especially on the presence of an "eschar" and positive serological test for scrub typhus.

Serologic assays (indirect fluorescent antibody, indirect immunoperoxidase and enzyme immunoassays) are the mainstays of laboratory diagnosis. PCR amplification of *Orientia* genes from eschars and blood also is effective.

Aims and objectives

Aims and objectives of the study were to bring forth the importance of scrub typhus as one of the common causes of acute febrile illness and as an uncommon cause of meningoencephalitis, to do a descriptive study of scrub typhus cases in the regions of South-Eastern Rajasthan, to describe clinical and biochemical parameters of meningoencephalitis due to scrub typhus collectively and along with acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), renal failure, dysrhythmia, life-threatening gastrointestinal (GI) hemorrhage and hepatitis considering meningo-encephalitis as one of the fatal complications in scrub typhus.

METHODS

A descriptive observational study of 39 diagnosed cases of scrub typhus admitted to SRG Hospital, Jhalawar for 6 months duration (May 2018 to October 2018) was conducted. Patients presenting with fever, altered sensorium were evaluated by non-contrast computed tomography (NCCT) brain followed by a lumbar puncture and the diagnosis of scrub typhus was confirmed by the enzyme-linked immunosorbent assay (ELISA) test along with other clinical and laboratory parameters. Data concerning the cases were recorded and analysed using appropriate statistics.

Inclusion criteria

All cases aged more than 18 years, having complaints of fever (with or without altered sensorium) who presented to our hospital, having diagnosed as scrub typhus by IgM ELISA positivity along with suggestive biochemical parameters and all other causes being ruled out. Based on the clinical features, cases were divided into two groups, those having CNS symptoms (s/o meningoencephalitis) and those who didn't have any CNS symptoms.

Exclusion criteria

Patients with the following were excluded: immunocompromised, leukemias, lymphomas, bleeding disorders, tuberculosis, connective tissue diseases, viral hepatitis, bacterial and viral meningoencephalitis, previous history of any neurosurgical procedure, chronic suppurative otitis media (CSOM), chronic liver and kidney disorder, undergoing psychiatry treatment or consultation.

Cases were divided based on the presence (CNS group) or absence of CNS symptoms (non-CNS group) and evaluated accordingly as per standard protocols. Routine investigations were sent for all the cases. Brain imaging and CSF analysis were done in the meningoencephalitis group. Numerical data were analyzed in the form of mean, standard deviation (SD) values and qualitative data in the form of proportions.

The two groups were compared by unpaired t test, Chi square, and p values were determined ($p<0.05$ was considered significant).

RESULTS

Amongst a total of 39 cases, 17 were males and the rest females.

In the group of meningoencephalitis, the male to female (M: F) ratio was 1.75:1, while the same ratio was 0.55:1 in the non-CNS group.

Table 1: Demographic data.

Variables	Frequency	Percent (%)
Age (years)		
17 to 20	5	12.8
21 to 30	5	12.8
31 to 40	12	30.8
41 to 50	4	10.3
51 to 60	4	10.3
More than 60	9	23.1
Total	39	100
Gender		
Male	17	43.6
Female	22	56.4
Total	39	100

The average duration of hospital stay was approximately 9±3days. Fever was documented in all cases and the mean duration of fever at the time of presentation was 5.61±3.08 days. While other symptoms were headache (97.4%), myalgia (94.8%), cough with expectoration (64.10%), GI complain (51.28%), altered sensorium (28.20%) and rash (43.58%).

The pathognomonic eschar was detected in 12 out of 39 patients (30.77%). The site of eschar was in various locations like inguinal, axilla, around the umbilicus, right shoulder.

The altered sensorium in the form of reduced level of consciousness, abnormal behaviors, agitation, irritability, or irrelevant talk was documented in all cases along with a headache of meningoencephalitis headache was reported be holocranial in the majority of cases. Glasglow coma scale (GCS) was normal in 28 cases (71.8%) while mild impaired in 4 (10.3%), moderate in 5 (12.8%), severe in two (5.1%) meningeal signs were present in 8 cases.

Table 2: Symptology of patient.

Signs and symptoms	Signs of meningitis		P
	Yes	No	
Headache	8	30	<0.607
Myalgia	8	29	<0.461
Cough with expectoration	4	21	<0.351
GI complaint	2	18	<0.095*
Altered sensorium	8	3	<0.000**
Rash	5	12	<0.226
Lymphadenopathy	1	10	<0.268
Hepatosplenomegaly	4	19	<0.563
Bleeding manifestation	1	0	<0.046*
Normal BP	5	26	<0.182
High BP	3	5	

*Significant and **highly significant.

Other features noted were lymphadenopathy (28.20%) icterus (43.58%), hepatosplenomegaly (58.9%) and bleeding manifestation (2.5).

On comparison of CNS and non-CNS groups clinically found that GI complaints were more in the non-CNS group (p<0.095) while altered sensorium and bleeding manifestation were common in the CNS group (repp-value p<0.000, 0.046).

The CNS group was more prone to develop acute kidney injury (AKI) (12.82%) compared to the non-CNS group.

Respiratory complications including pleural effusion, pneumonia, and ARDS were more in CNS group of patients.

Decreased total protein (<0.000), decreased albumin (<0.009), total bilirubin (<0.005), predominantly direct bilirubin (<0.001), electrolyte imbalance was found more in CNS group of patients.

Severe thrombocytopenia and hypoalbuminemia are important prognostic factor for developing complicated scrub typhus.

CSF analysis was done in 8 patients of scrub typhus with clinical suspicion of meningitis/meningoencephalitis, after fundus examination. CSF analysis finding along with other neurological features and patients' outcome of all patients are shown in Table 3.

The mean CSF protein, glucose, and cell count were 83.54 mg/dl, 54.72 mg/dl and 77.81 cells/cumm of CSF respectively with lymphocyte count of more than 90% in all except one. Most patients had lymphocytic pleocytosis and mean lymphocyte percentage was 90.9 cells/mm. Neuroimaging in the form of NCCT scan was done in 8 patient, 4 patient had no significant abnormalities in NCCT brain while 3 of them had meningeal enhancement and 1 patient showed hypodensity in frontoparietal lobe (vasculitis and magnetic resonance imaging (MRI) was suggested to rule out). Among the major non neurological complications; 2 (5.1%), 7 (17.9%) and 17 (43.58%) had ARDS, AKI and hepatitis respectively. All cases of scrub typhus were treated with tablet doxycycline. Azithromycin was added especially for patients with CNS involvement in case of delayed recovery.

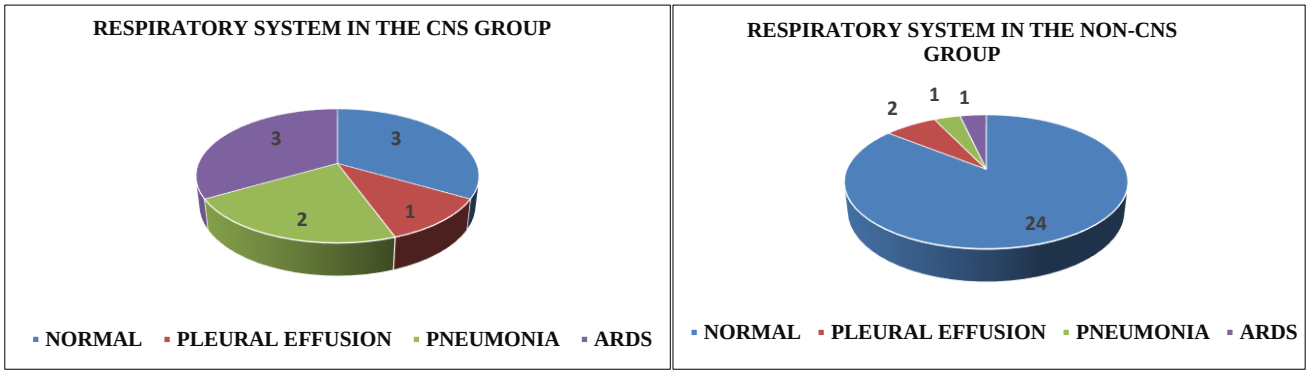

Figure 1: Comparison between CNS and non-CNS group.

Chi-square=10.306, df=3 and p<0.016 (significant)

Table 3: Picture of CSF analysis.

Parameters	Frequency	Percent	Mean	Maximum	Minimum	Standard deviation
CSF protein (mg/dl)						
Normal (15-45)	2	18.2	83.5455	143.00	49.00	27.28869
Increased	9	81.8				
CSF sugar (mg/dl)						
Normal (45-85)	6	54.5	54.7273	119.00	23.00	30.10678

Continued.

Parameters	Frequency	Percent	Mean	Maximum	Minimum	Standard deviation
Decrease	5	45.5				
CSF total count (cells/hpf)						
Mild elevated (5-200)	9	81.8	77.8182	250.00	13.00	77.49815
Moderate elevated (>200)	2	18.2				
CSF neutrophils (%)						
>50	1	9.1				
<50	10	90.9				
CSF lymphocytes (%)						
>50	10	90.9				
<50	1	9.1				

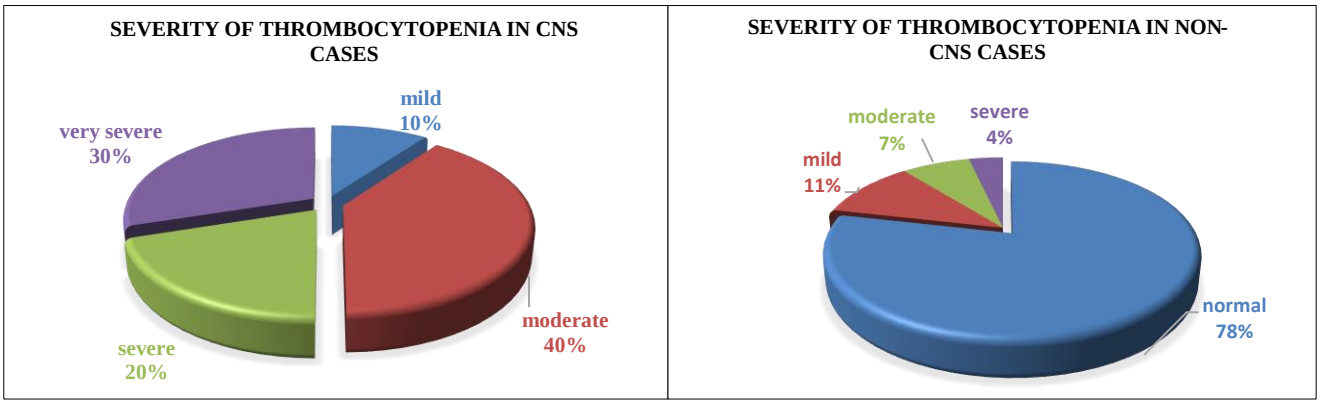

Figure 2: Comparison between thrombocytopenia in CNS and non-CNS group.

Chi-square=14.905, df=4 and p<0.005 (highly significant).

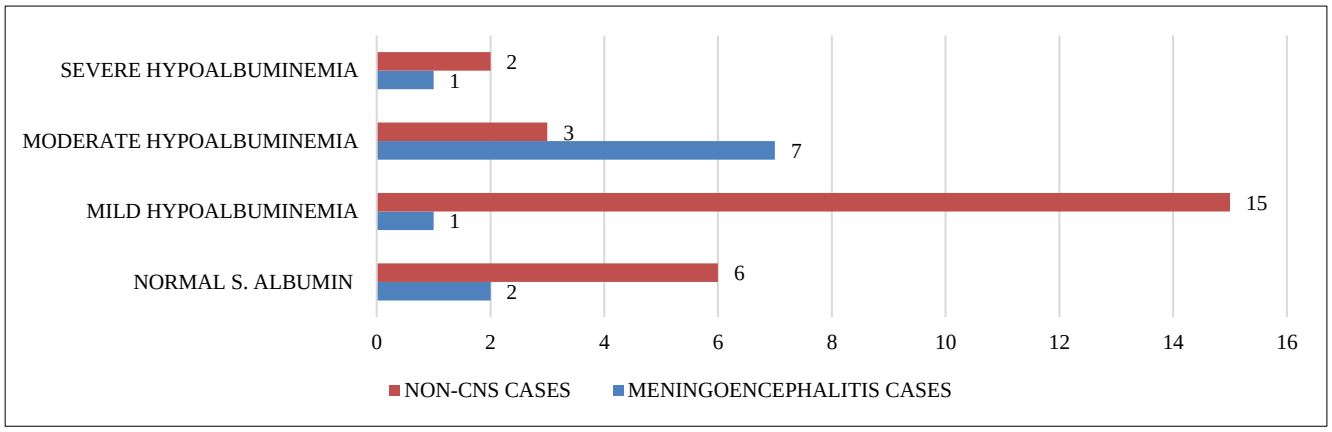

Figure 3: Incidence of hypoalbuminemia amongst the two groups of scrub typhus.

Chi-square=15.503, df=3 and p<0.009 (highly significant).

DISCUSSION

Acute febrile illness with CNS symptom requires timely diagnosis and treatment to prevent mortality and sequelae. CNS involvement is almost reported in all rickettsial diseases such as rocky mountain spotted fever, epidemic typhus, murine typhus, scrub typhus and Q fever.[8-11] Depends on the predominant cellular target *Rickettsia rickettsii* and *Rickettsia prowazekii* had predominant CNS manifestation as encephalitis, but *O. tsutsugamushi* and *Coxiella burnetii* predominantly manifested as meningoencephalitis.[1]

The pathognomic eschar that helped in early diagnosis of patients was detected in 30.77% patients.

Eschars were reported from 20% to 86% of patients in different studies.[6,12,13] One study from North-Eastern India showed the higher percentage in children than the adult population.[14,15]

Identification of eschar may be difficult in Indian population due to their dark skin and it was also expected to be less in areas endemic for scrub typhus. The absence of eschar was a risk factor for mortality in a study.[16]

The results had shown the profile of scrub typhus meningoencephalitis from an area already well-known for scrub typhus. The mean duration of fever was 5.61±3.08 days prior to the presentation. This was shorter than the mean duration of fever of 7.68 and 8.4 days reported from another study and its duration was longer than that of viral encephalitis or acute bacterial meningitis.[3,12]

Headache and myalgia were a common symptom in scrub typhus. In the present study, headache was present in all cases similar to one study and was nonspecific in nature in the majority of cases. Other studies had reported the occurrence of headache in around 46-77% of patients.[3,5,12] Headache may also occur in scrub typhus patients without meningitis.[5,12] But it was less severe and did not have other CNS symptoms. Sign of meningeal irritation in the form of neck rigidity and/or Kernig's sign were cardinal clinical features of any meningitis. In the present study, meningeal signs were present in 76.92% of patients though other studies shown the presence of neck rigidity in 45.45% and 49% of case.[12,13] In the present study altered sensorium was seen in all patients similar to finding of one study, but others reported lower incidence of about 56.3%.[3,13] This may be due to the severity of the cases in our series or referral bias.

Hepatitis and hepatomegaly were the most common associated abnormalities in our study. AKI was a common complication of scrub typhus with poor outcome.

CSF analysis in scrub typhus meningoencephalitis usually revealed mild to moderate elevation in protein, low to normal glucose and a mild degree of lymphocytic pleocytosis. The absence of neutrophilic pleocytosis helped in differentiating it from bacterial meningitis but differentiating it from tubercular meningitis remained difficult. The present study showed similar finding except in few cases where no pleocytosis was noted. Tubercular meningitis remained the closest differential diagnosis in our setting. Staining for acid-fast bacilli (AFB) in CSF had low sensitivity and CSF culture for AFB take up to 8 weeks and was positive in only 50-75% of the cases.[17] Markers like CSF ADA may be helpful in differentiating scrub meningitis from tubercular meningitis as mentioned in some studies. But, in present CSF ADA was found to be elevated in almost all cases (>10 U/l) for whom CSF ADA report was available and did not help in differentiating scrub typhus meningoencephalitis from tubercular.[18]

Doxycycline was the drug of choice. However, doxycycline was bacteriostatic to *O. tsutsugamushi* and did not cross the blood-brain barrier beyond 15-30%.[19] Sometimes progressive neurological damage had occurred in spite of treatment with doxycycline.[20] Due to resistance, immune mediated injury or due to drug interaction with oral antacids.[21] Injectable azithromycin was a good alternative for condition where doxycycline is contraindicated or having doubtful gastrointestinal absorption.[22] Recovery was good in scrub typhus meningoencephalitis with appropriate therapy and patient usually showed sign of improvement within 48 hours of initiation of specific therapy.

Limitations

Scrub IgM can be negative with some serotypes and hence cases of probable scrub typhus responsive to doxycycline that were excluded could have contributed more sample size to the study. Differences in severity or differences in virulence occur among various serotypes. So, confirming whether meningitis was caused only by some serotypes would have been an ideal approach. A comparative study analyzing scrub typhus induced meningoencephalitis and other common causes of meningoencephalitis would give more insights into the topic.

CONCLUSION

Meningoencephalitis although a rare entity is a common complication among scrub typhus patients. Thrombocytopenia and hypoalbuminemia are more commonly found among the cases who presented with CNS symptoms. Scrub typhus having CNS involvement responded well to a combination of doxycycline and azithromycin resulting in early defervescence and decreased hospital stay (although both doxycycline and azithromycin are proven equally efficacious). Scrub typhus should be an important differential diagnosis in all patients with an acute febrile illness with thrombocytopenia, elevated liver enzymes with or without altered sensorium.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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