Original Article

Differential diagnosis of scrub typhus meningitis from bacterial meningitis using clinical and laboratory features

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Abstract

Background: Central nervous system (CNS) 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:** To identify the clinical and laboratory parameters that may help in differentiating scrub typhus meningitis from bacterial meningitis. **Setting and Design:** This is a cross-sectional analysis of adult patients admitted with scrub typhus and bacterial meningitis to a tertiary care teaching institute in South India. **Materials and Methods:** A comparison of clinical and laboratory features of 25 patients admitted with meningitis to a university teaching hospital during a 15-month period was made. These patients had meningitis diagnosed based on abnormal cerebrospinal fluid (CSF) analysis with either positive IgM scrub typhus ELISA serology (n = 16) or with CSF culture isolating bacteria known to cause bacterial meningitis (n = 9). The clinical and laboratory features of the patients with scrub typhus meningitis and bacterial meningitis were compared. **Results:** The mean age was similar in the scrub typhus and bacterial meningitis groups (44.0 ± 18.5 years vs. 46.3 ± 23.0 years). Features at admission predictive of a diagnosis of scrub typhus meningitis were duration of fever at presentation >5 days (8.4 ± 3.5 days vs. 3.3 ± 4.2 days, $P < 0.001$), CSF white cell count of a lesser magnitude (83.2 ± 83.0 cells/cumm vs. 690.2 + 753.8 cells/cumm, $P < 0.001$), CSF lymphocyte proportion >50% (83.9 ± 12.5% vs. 24.8 ± 17.5% $P < 0.001$), and alanine aminotransferase (ALT) elevation more than 60 IU (112.5 ± 80.6 IU vs. 35 ± 21.4 IU, $P = 0.02$). **Conclusion:** This study suggests that clinical features, including the duration of fever and laboratory parameters such as CSF pleocytosis, CSF lymphocyte proportion >50%, and ALT values are helpful in differentiating scrub typhus from bacterial meningitis.

Key words: *Aseptic, differential diagnosis, meningitis, scrub typhus*

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Introduction

Acute meningitis and encephalitis are medical emergencies that require prompt evaluation and management. Scrub typhus, caused by *Orientia tsutsugamushi*, commonly manifests as acute febrile illness with multi-system involvement and meningitis or meningoencephalitis can occur in up to a fifth of

affected patients. Neurological involvement can, in fact, often be a prominent clinical manifestation of scrub typhus.[1-3] Scrub typhus, which is endemic in many parts of Southeast Asia, is now well documented as re-emerging in the Indian subcontinent.[4-6] Reports of this infection are becoming increasingly common in travelers to Asia as well.[7] The magnitude of this problem continues to be underestimated in many endemic areas, especially in India where scrub typhus is fast becoming as an important cause of acute meningitis. The relatively unique propensity of O. *tsutsugamushi* to cause by infecting vascular endothelial cells results in multiple organ dysfunction in scrub typhus. Direct invasion of central nervous system (CNS) by the organism based on polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) has been conclusively shown.[8] However, scrub typhus meningitis remains an unclear entity, and clinical features differentiating meningitis due to scrub typhus from other forms of acute bacterial and viral meningitides are often lacking. The pathognomonic eschar, indicative of chigger (the vector) bite, though helpful if found, is present in less than 50% of patients with scrub typhus.[9,10] Additionally, the laboratory methods specific for scrub typhus remain inadequate or inaccessible in most parts of the developing world. These factors often contribute to a delay in the diagnosis of scrub typhus meningitis and encephalitis with the associated higher mortality.The aim of this study is to identify the clinical and laboratory parameters that may be helpful in differentiating scrub typhus from common acute bacterial meningitis.

Materials and Methods

All patients aged 16 years or above, hospitalized with a diagnosis of scrub typhus in a large university teaching hospital in South India over a 15-month period were considered for inclusion in the study.The diagnosis of scrub typhus was confirmed by serum IgM enzyme-linked immunosorbent assay (ELISA). Among the confirmed scrub typhus cases, CSF analysis 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. CSF samples were also inoculated for bacterial, mycobacterial, and fungal cultures. Patients who were IgM ELISA positive for *O. tsutsugamushi* and had features suggesting meningitis on CSF analysis, and in whom other causative organisms were not found on stains or cultures, were defined as scrub meningitis cases. Those patients hospitalized during the same period with a diagnosis of acute meningitis, but with CSF culture isolating a bacterial pathogen known to cause bacterial meningitis, were included as controls. The clinical and laboratory features of patients with scrub typhus meningitis and bacterial meningitis were compared.

Statistical analysis was performed using SPSS software for Windows version 11.0. Descriptive data are given as mean (SD) or as median (range). Chi-square test was used to compare dichotomous variables and Mann–Whitney test was used for continuous variables. Logistic regression analysis was performed to predict the diagnosis of scrub typhus meningitis. A P value < 0.05 was considered statistically significant.

Results

During the study period, there were 82 cases of scrub typhus of which 16 had meningitis or meningoencephalitis caused by *O. tsutsugamushi*. Nine of these cases were males and seven were females. The majority of the patients were farmers or housewives (72%). The most frequent presenting complaints were fever (100%), headache (81.3%), and nausea and vomiting (75%). The pathognomonic eschar was found in only three patients (18.6%).

The control group was comprised of nine patients diagnosed to have bacterial meningitis: Eight with Streptococcus pneumoniae and one with Group B Streptococci. The clinical and laboratory features of the cases and the controls are presented in Table 1.

Table 1: Clinical and laboratory features

Parameter	Scrub typhus meningitis (*n*=16) (%)	Bacterial meningitis (*n*=9)(%)	*P* value
Age	44.0±18.5	46.3±23.0	0.934
Duration of fever (days)	8.4±3.5	3.3±4.2	<0.001
Headache	13 (81.3)	8.0 (88.9)	1.000
Nausea/Vomiting	12 (75)	6 (66.7)	0.673
Seizure	4 (25)	1 (11.1)	0.621
Altered sensorium	9 (56.3)	8 (88.9)	0.182
Cough	3 (18.8)	1 (11.1)	1.00
Breathlessness	4 (25)	0	0.26
GCS	12±4.0	10±3.4	0.121
Tachypnoea	7 (43.8)	2±22.2	0.401
Jaundice	5 (31.3)	0	0.123
CSF TC (cells/cumm)	83.2±83.0	690.2±753.8	<0.001
Poly (%)	16.1±12.5	75.2±17.5	<0.001
Lymph(%)	83.9±12.5	24.8±17.5	<0.001
Glucose (mg/dl)	81.3±44.5	21.8±13.5	<0.001
Protein (mg/dl)	106.9±66.7	555.8±250.9	<0.001
Creatinine (mg/dl)	1.5±1.05	1.2±0.5	0.889
TC (cells/cumm)	15981.3±12954.0	12533.3±6057.8	0.803
Platelets (cells/cumm)	116125±70430.9	205250±81920	0.064
Aspartate aminotransferase	201.7±133	123.5±121.7	0.202
Alanine aminotransferase′	112.5±80.6	35±21.4	0.023
Chest X-ray abnormality	6 (40)	1 (11.1)	0.191

GCS = Glasgow coma scale, CSF = Cerebrospinal fluid

The duration of fever prior to presentation was significantly longer in the scrub typhus group as compared to the bacterial meningitis group (8.4 ± 3.5 days vs. 3.3 ± 4.2 days, $P < 0.001$). The scrub typhus cases were also less likely to present with an altered sensorium (56.3 vs. 88.9%), and their degree of obtundation was generally less (mean Glasgow Coma Scale (GCS) score (12 ± 4.0 vs. 10 ± 3.4)); however, these differences were not found to be statistically significant. Signs of raised intracranial pressure were uncommon in both groups, with only one patient among scrub typhus cases demonstrating bilateral papilledema and radiological features of generalized cerebral edema on noncontrast enhanced computed tomography (CT) scan of the brain. Focal neurological signs were also noted to be rare with only one patient developing hemiparesis among scrub typhus cases in addition to the above presenting features. A CT imaging of the brain in this case showed an internal capsule infarct. No other underlying causative risk factors for the infarct could be determined on clinical and laboratory evaluation.

Serum laboratory findings on admission were notable for a higher degree of alanine aminotransferase (ALT) elevation in the scrub typhus meningitis group, with most of the control group having normal or near normal values. (112.5 ± 80.6 IU vs. 35 ± 21.4 IU, $P = 0.023$). Hepatic involvement with ALT > 60 IU was seen in 75% of the patients with scrub typhus meningitis. Leukocytosis was present in both groups (12533 +/- 6058 vs 15981 +/- 12954; P=0.803) with no significant difference between the two.

CSF findings between the two groups were markedly different. The study cases had CSF pleocytosis of a lesser magnitude (83.2 ± 83.0 cells/cumm vs. 690.2 ± 753.8 cells/cumm, $P < 0.001$), a higher proportion of lymphocytes in the CSF (83.9 ± 12.5 vs. 24.8 ± 17.5%, $P < 0.001$), a lesser degree of protein elevation (106.9 ± 66.7 vs. 555.8 ± 250.9; $P < 0.001$), and a higher CSF sugar level (81.3 ± 44.5 mg% vs. 21.8 ± 13.5 mg%, $P < 0.001$).

Discussion

The purpose of this study was to characterize scrub typhus meningitis and meningoencephalitis in an endemic area and to suggest clinical and basic laboratory findings that may permit earlier differentiation from bacterial meningitis. The results of our study indicate several potentially useful distinguishing features. While the majority of typical presenting symptoms were not significantly different, including headache, alterations in mental status, GCS score, and occurrence of seizure, the duration of fever prior to presentation (mean 8.4 days) was significantly longer in patients with scrub typhus. Because of multi-organ system involvement in scrub typhus, other signs and symptoms, such as breathlessness, tachypnea, cough, and jaundice were often present in scrub typhus patients, but not to a significant degree. Notably, none of the control group experienced breathlessness or were noted to be jaundiced. In our study populations, papilledema was only seen in one patient (5%), while it has been previously documented in up to a fifth of patients with scrub typhus, if untreated.[11] This may represent a difference in time to diagnosis and treatment or variation in the strain of the organism causing the infection. Autopsy studies on patients with scrub meningitis have shown diffuse or focal mononuclear cell exudates in the leptomeninges and typhus nodules that are distributed throughout the brain parenchyma.[12,13]

Many of the standard laboratory findings were not significantly different between the two groups. Thrombocytopenia did trend toward being significantly different ($P = 0.06$). This may be reflective of the small number of patients in this study or that thrombocytopenia tends to be mild with scrub typhus.[9] A serum ALT elevated to more than 60 IU was, however, strongly associated with scrub typhus meningitis. A mild rise in these enzymes is found in the majority (66.7 to greater than 90%) of patients with scrub typhus in multiple studies, holding true in meningitis cases as well.[9,10] The CSF analysis of scrub typhus cases showed significantly less pleocytosis, a lymphocyte proportion greater than 50%, and a lesser degree of protein elevation than in those cases with bacterial meningitis. Similar to our results, Silpapojakul, *et al.*, in a case series of nine patients with scrub typhus and three with murine typhus meningitis and/or meningoencephalitis, reported a predominantly mononuclear CSF pleocytosis with a lower total WBC counts (<150 cells/cumm). They also documented a mean duration of symptoms prior to hospitalization 9 days, similar to the findings in this study.[14] Among our control patients, who were predominantly infected by pneumococcal meningitis, the degree of CSF pleocytosis was less than has been previously reported.[15] Our report of a statistically significantly lower CSF WBC count may, thus, actually be more significant than found in this study.

The overall mortality rate for our patients with scrub typhus meningitis was 25%. As with other forms of meningitis, a high index of suspicion with establishing an early diagnosis and prompt treatment will reduce case fatalities. Notably, two out of the four patients who expired in our studies were treated appropriately with doxycycline. Although antibiotic resistance, including to doxycycline, has been reported in northern Thailand, it is presumed to be rare in south India.[16,17] There is some concern that doxycycline may fail to achieve adequate concentration in the CSF at conventional doses.

Rifampicin has been shown to be effective compared to doxycycline for scrub typhus infections acquired in northern Thailand.[17] However, the use of rifampicin for scrub typhus in areas where tuberculosis is also endemic raises larger concern for resistant tuberculosis, and therefore is not recommended.

Tuberculous meningitis also possesses an additional diagnostic challenge with patients presenting with a subacute onset of meningitis, as both tuberculous meningitis and scrub typhus meningitis tend toward a lymphocyte-predominant CSF. However, slightly lowered CSF glucose and presence of focal signs in tuberculous meningitis may help in differentiating it from scrub typhus meningitis. Additionally, the elevated transaminases provide a clue for scrub typhus infections, which would be unusual in tuberculous meningitis unless they were already on treatment. Scrub typhus meningitis also needs to be differentiated from aseptic meningitis. Although this study clearly characterizes scrub typhus meningitis and provides differentiating features compared to bacterial meningitis, one of the main limitation is the absence of comparison with other close differentials like tuberculous meningitis and viral meningoencephalitis.

In conclusion, scrub typhus is a re-emerging cause of acute and subacute meningitis, which can be difficult to diagnose. The eschar, a pathognomonic 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 patient. Serological testing using IgM ELISA continues to be the mainstay in the laboratory diagnosis of scrub typhus, but microimmunoflourescence, although considered the test of choice, is not commonly used due to the expenses involved. These serologic tests are available only in major reference laboratories in many endemic countries, and the more commonly available Weil–Felix test lacks both sensitivity and specificity. Until better point-of-care testing is available, the clinical and available laboratory features of this infection are often the most useful parameters for diagnosis.

Our study, although small in nature, provides a helpful clinical picture to help clinicians differentiate this disease, which carries a relatively high mortality rate. We suggest from our data a few clinical and laboratory variables that may help in distinguishing scrub typhus meningitis from bacterial meningitis in order to facilitate early initiation of appropriate antibiotics. Our study, however, is limited by its size, and further research, on a larger scale, is warranted for this deadly disease.

References

1. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. BMC Infect Dis 2010;10:108.
2. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. J Assoc Physicians India 2010;58:24-8.
3. Dass R, Deka NM, Duwarah SG, Barman H, Hoque R, Mili D, *et al*. Characteristics of pediatric scrub typhus during an outbreak in the North Eastern region of India: Peculiarities in clinical presentation, laboratory findings and complications. Indian J Pediatr 2011;78:1365-70.
4. Kelly DJ, Fuerst PA, Ching WM, Richards AL. Scrub typhus: The geographic distribution of phenotypic and genotypic variants of Orientia tsutsugamushi. Clin Infect Dis 2009;48:S203-30.
5. Mathai E, Rolain JM, Varghese GM, Abraham OC, Mathai D, Mathai M, *et al*. Outbreak of scrub typhus in southern India during cooler months. Ann N Y Acad Sci 2003;990:359-64.
6. Kularatne SA, Edirisingha JS, Gawarammana IB, Urakami H, Chenchittikul M, Kaiho I. Emerging rickettsial infections in Sri Lanka: The pattern in the hilly Central Province. Trop Med Int Health 2003;8:803-11.
7. Jensenius M, Fournier PE, Raoult D. Rickettsioses and the international traveler. Clin Infect Dis 2004;39:1493-9.
8. Pai H, Sohn S, Seong Y, Kee S, Chang WH, Choe KW. Central nervous system involvement in patients with scrub typhus. Clin Infect Dis 1997;24:436-40.
9. Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, *et al*. Scrub typhus: An unrecognized threat in South India-clinical profile and predictors of mortality. Trop Doct 2010;40:129-33.
10. Mahajan SK, Rolain JM, Kashyap R, Bakshi D, Sharma V, Prasher BS, *et al*. Scrub typhus in the Himalayas. Emerg Infect Dis 2006;12:1590-2.
11. Scheie HG. Ocular changes associated with scrub typhus: A study of 451 patients. Arch Ophthalmol 1948;40:245-67.
12. Allen AC, Spitz S. A comparative study of the pathology of scrub typhus (Tsutsugamushi disease) and other rickettsial diseases. Am J Pathol 1945;21:603-81.
13. Settle EB, Pinkerton H, Corbett AJ. A pathological study of tsutsugamushi disease (scrub typhus) with notes on clinicopathological correlation. J Lab Clin Med 1945;30;639-61.
14. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. Arch Intern Med 1991;151:1753-7.
15. De Gans J, Van de Beek D. The European dexamethasone in adulthood bacterial meningitis study investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.
16. Watt G, Chouriyagune C, Ruangweerayud R, Watcharapichat P, Phulsuksombati D, Jongsakul K, *et al*. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. Lancet 1996;348:86-9.
17. Watt G, Kantipong P, Jongsakul K, Watcharapichat P, Phulsuksombati D, Strickman D. Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: A randomised trial. Lancet 2000;23;1057-61.

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