Original Article

Scrub typhus meningitis: An under-recognized cause of aseptic meningitis in India

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ABSTRACT

Background: Central nervous system (CNS) involvement in scrub typhus is seen in up to a quarter of patients. However, the literature on cerebrospinal fluid (CSF) analysis and outcome in meningitis/meningo-encephalitis due to scrub typhus is scant.

Materials and Methods: This retrospective study included patients who were admitted to a medical college hospital with scrub typhus meningitis/meningo-encephalitis between 2005 and 2011. The clinical and laboratory profile, details of CSF analysis and outcome were documented.

Results: The study included 189 patients with meningitis/meningo-encephalitis due to scrub typhus. The mean age of the patients was 41 ± 4 years. The mean duration of fever before presentation was 9.4 ± 3 days. The common presenting complaints were headache (64.2%), nausea/vomiting (60%), altered sensorium (53.7%) and seizures (22.1%). The presence of an eschar was documented in 27.5% of the patients. The mean CSF white blood count was 80 cells/cu mm (range: 5–740). There was a clear lymphocyte predominance (mean 87.6%). The mean CSF protein level was 105 mg% (range: 13–640). The mean CSF sugar level was 63.9 mg% (range 25–350), and was less than 40 mg% in 11.1% of the cases. The case fatality rate was 5.8% (11/189). Univariate analysis showed the presence of an eschar (15.4% vs 2.2%; Odds Ratio [OR]: 8.1) and altered sensorium (9.8% vs 1.1%; OR: 9.2) to be significant predictors of mortality.

Conclusions: In endemic regions, scrub typhus should be considered in the differential diagnosis of aseptic meningitis. Modest elevation of cells in the CSF with lymphocytic pleocytosis and multi-organ involvement may indicate scrub typhus meningitis/meningo-encephalitis.

Key words: Central nervous system; meningitis; scrub typhus

Introduction

Scrub typhus is a vector-borne bacterial infection caused by *Orientia tsutsugamushi* and is commonly seen in the geographic area known as the "tsutsugamushi triangle," which extends from northern Japan and Far East Russia in the north, to northern Australia in the south, and to Pakistan and Afghanistan in the west. It is a zoonotic disease and is widely prevalent in areas with heavy monsoon and an agrarian way of life. The usual presentation is that of a short-duration fever, headache, myalgia and varying involvement of the major organs. *O. tsutsugamushi* infects the endothelium of the small blood vessels resulting in severe complications such as acute respiratory distress syndrome (ARDS), hepatitis, renal failure, meningo-encephalitis and myocarditis with shock in a varying proportion of patients. Central nervous system (CNS) involvement is often a prominent clinical manifestation in scrub typhus infection, and meningitis or meningo-encephalitis occurs in 12.5–26% of the affected patients.[1,2] The name "typhus" itself is derived from the Greek word "typhos," which means "stupor." In endemic areas, scrub typhus is becoming an increasingly important cause of meningitis/meningo-encephalitis. The causative agent appears to enter the CNS via infected monocytes during

Access this article online	
Website: www.neurologyindia.com	Quick Response Code
DOI: 10.4103/0028-3886.156282	

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the phase of meningeal inflammation or by invading the endothelium through the luminal membrane. They are then released, via the basal cell membrane, into the perivascular space.[3] However, in the absence of a pathognomonic eschar, scrub typhus meningitis/meningo-encephalitis can remain undetected, and is often wrongly treated as pyogenic, viral or tuberculous meningitis. The index of suspicion for scrub typhus meningitis is low and the data on cerebrospinal fluid (CSF) analysis is scant. The aim of this study is to describe the clinical features, the CSF analysis and the outcome in a large cohort of patients with scrub typhus meningitis.

Materials and Methods

This retrospective study was carried out at the Christian Medical College, Vellore, a 2700-bed medical college hospital, between October 2005 and December 2011. All adult patients with the diagnosis of scrub typhus and meningitis were included in the study.

The diagnosis of scrub typhus was confirmed by immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) positivity and/or the presence of a pathognomonic eschar with polymerase chain reaction (PCR) confirmation where feasible. The IgM ELISA was performed on serum samples using Scrub Typhus Detect (InBios International Inc., Seattle, WA, USA) as per the manufacturer's instructions. An optical density (OD) >0.5 was considered positive. A standard PCR targeting the 56-kDa outer membrane protein genes was carried out in a subset of cases for the diagnostic confirmation of scrub typhus. As scrub typhus shares the same clinico-epidemiological features as that of malaria, dengue, enteric fever and other bacterial infections, they were considered in the differential diagnosis and patients were excluded from the study if any of the above infections were proven.

Meningitis was suspected and CSF analysis (for cell counts and levels of protein and sugar) was performed if the patient had one or more of the following clinical features: Headache, nausea/vomiting, seizure, altered sensorium or nuchal rigidity. In addition, the centrifuged CSF sample was subjected to gram stain and inoculated for bacterial cultures. PCR for Herpes simplex virus and mycobacterial and fungal cultures were performed when clinically suspected, to rule out other causes of meningitis/meningo-encephalitis. Patients in whom CSF analysis could not be performed were excluded from the study.

The clinical and laboratory profiles, details of CSF analysis and outcomes were documented. Factors associated with mortality were analyzed using univariate and multivariate logistic regression analysis.

Statistical methods

Statistical analysis was performed using SPSS software for Windows version 16.0. Descriptive data are given as mean (SD) or as range. Chi-square test or Fisher exact test was used to compare categorical variables and *t*-test or Mann–Whitney test was used for continuous variables as appropriate. The association of CSF analysis with the outcome was analyzed by univariate analysis, and their 95% confidence intervals were calculated. For all tests, a two-sided *P* value of 0.05 or less was considered statistically significant.

This study was approved by the Institutional Review Board of the Christian Medical College, Vellore and patient confidentiality was maintained using unique identifiers.

Results

Baseline clinical characteristics

The study included 189 cases of scrub typhus admitted with meningitis/meningo-encephalitis during the study period [Figure 3]. Majority of the patients were from Tamil Nadu (62.4%) and the neighboring state of Andhra Pradesh (35.4%). The mean age of the patients was 41 ± 16.3 years, and there was a slight male predominance (56.8%). Hypertension and diabetes mellitus were associated features in 10.5% and 9.4% of the patients, respectively. The mean duration of fever before presentation was 9.3 ± 4.8 days. The presence of an eschar was documented in 27.3% (52/189) of the patients, with the common sites being the groin, genitalia, axilla, neck and inframammary folds. The most common presenting complaints were headache (64.2%), nausea/vomiting (60%), altered sensorium (53.7%) and seizures (22.1%) [Table 1].

The mean total peripheral white blood cell count (WBC) was 11,112.0 ± 4229.7 cells/cu mm while the mean platelet count was 1,22,560 ± 86,100 cells/cu mm. The platelet count was <1,00,000 cells/cu mm in 91/189 (48.1%) patients. Hepatic involvement (serum bilirubin >2 mg/dL or three-fold elevation of Serum Glutamic Oxaloacetic Transaminase (SGOT)/Serum Glutamic Pyruvate Transaminase (SGPT) was seen in 59.6% of patients, pulmonary involvement (PaO_2/FiO_2 ratio <300 or need for ventilator assistance) in 19.7% of patients, and renal dysfunction (serum creatinine >2 mg/dL or need for dialysis) in 18.6% of patients. Cardiovascular involvement in the form of hypotension or requirement of ionotropic support was seen in 15% of the patients.

CSF cell count analysis

The mean CSF WBC count was 80 ± 120 cells/cu cc (range 5–900 cells) [Table 1]. More than 2/3rd of the cases had CSF WBC count up to 100 cells/cu cc, while only 10.5% (20/189) of

Table 1: Patient characteristics, laboratory investigations and CSF analysis

Variable	Scrub typhus with meningitis (*N*=189)
Age, mean years (SD)	41±16.3
Gender: Male/female	108/81
Duration of illness, mean days (SD)	9.3±4.8
Pre-morbid illness	**Number (%)**
Diabetes mellitus	18 (9.4)
Hypertension	20 (10.5)
Clinical symptoms and signs	**Number (%)**
Headache	122 (64.2)
Nausea/vomiting	114 (60)
Altered sensorium	102 (53.7)
Seizures	42 (22.1)
Eschar	52 (27.4)
Laboratory investigations	**(Mean±SD)**
Total WBC count (cells/cumm)	11,112±4,229.7
Platelet count (cells/cumm)	1, 22,560±86,100
Total bilirubin (mg/dl)	2.13±2.37
Serum creatinine (mg %)	1.46±1.1
CSF analysis	**(Mean±SD)**
CSF WBC count (cells/cumm)	80±120.7
CSF lymphocytes (%)	87.6%
CSF protein (mg %)	105.9±80.9
CSF glucose (mg %)	69.4±89.6

WBC - White blood cell count, SD - Standard deviation, CSF - Cerebrospinal fluid

the patients had counts exceeding 200 cells/cu cc [Figure 1]. Lymphocyte was the major cell type on the differential count (87.6%). In this study, we observed that the mean CSF WBC counts were higher on the 2nd, 8th and 12th days after the onset of illness, and gradually decreased by the 13th day onwards [Figure 2]. The CSF WBC count was considered high if it was greater than or equal to an arbitrary cut off level of 100 cells/cu cc. A higher CSF cell count was significantly associated with correlates including a lower age group (36.0 years versus (vs) 42.1 years, *P* value = 0.03), a higher CSF protein level (136.2 gm% vs 97.3 gm%, *P* value = 0.019) and a higher peripheral WBC count (12,600 cell/cu cc vs 10,700 cells/cu cc, *P* value = 0.009).

The mean CSF WBC count among those patients with an eschar was 87.6 cells/cu cc (SD 123) as compared with 78.4 cells/cu mm (SD 120.7, 95% CI -30.1 to 48.6) in patients without it. Thus, there was no significant difference in the CSF cell response among patients with an eschar [Table 2]. Similarly, no significant correlation was found between CSF cell count and altered sensorium, seizures, headache, platelet count, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase or requirement of ventilation (data not shown).

CSF protein and glucose level analysis

The mean CSF protein level was 105.9 ± 80.9 (range 13–640 mg%), and was more than 100 mg% in 38% (72/189) of the patients. The mean CSF sugar level was 69.4 ± 89.6 mg% (range 25–350 mg%), and was less than 40 mg% in 11.1% of the cases [Figure 1]. The CSF glucose level was not statistically different among those with altered sensorium (74.9 ± 103 mg% vs 62.5 ± 37.1 mg%, *P* value = 0.3) or those who had seizures (68.0 ± 32.1 mg% vs 69.5 ± 94.5 mg%, *P* value = 0.3).

Treatment and outcome

The patients were treated with doxycycline with or without intravenous azithromycin for a total duration of 7 days. The mean duration of hospital stay was 6.9 days (SD 5.1 days). Out of 189 patients, 11 patients died (5.8%). Univariate analysis showed the presence of an eschar (15.4% vs 2.2%; *P* = 0.002; OR: 8.1) and altered sensorium (9.8% vs 1.1%; *P* = 0.012; OR: 9.2) as being significantly associated with a higher mortality. The mean CSF protein level was significantly higher among the expired group as compared with those who were alive (253.5 ± 191.3 mg% vs 96.8 ± 58.8 mg%, 95% CI 27.9–285.4). The mean CSF WBC count and glucose levels were similar in both the groups.

Discussion

To the best of our knowledge, this is the largest descriptive study describing the details of CSF analysis in the presence of meningitis/meningo-encephalitis due to scrub typhus. Our study showed that the CSF WBC counts are usually modestly elevated but that the range can be very wide. A similar elevation and a broad range have been observed with the CSF protein levels as well.

Scrub typhus affects almost a million people every year, and mainly occurs in populations that encounter scrub vegetation as a part of their occupation or daily life. It has been reported from more than half of the Indian states (Jammu and Kashmir, Himachal Pradesh, Haryana, Rajasthan, West Bengal, Sikkim, Uttaranchal, Assam, Arunachal Pradesh, Nagaland, Maharashtra, Karnataka, Andhra Pradesh, Kerala, Tamil Nadu and Pondicherry) and has been found to account for up to 50% of undifferentiated febrile illnesses that occur in some parts of India during the cooler months of the year.[2] A variety of strains of *O. tsutsugamushi* are known to exist, and may contribute to the variation in presentation and outcome. Of the more than 30 antigenically different serotypes, the common ones are Gilliam, Karp, Kato, Shimokoshi, Kawasaki and Kuroki.[4]

Scrub typhus involves multiple organs, and both central and peripheral nervous system involvement is relatively common. The PCR studies on the CSF have conclusively proven direct invasion of the CNS by the organism.[3] The pathological CNS findings in the affected patients include a diffuse or

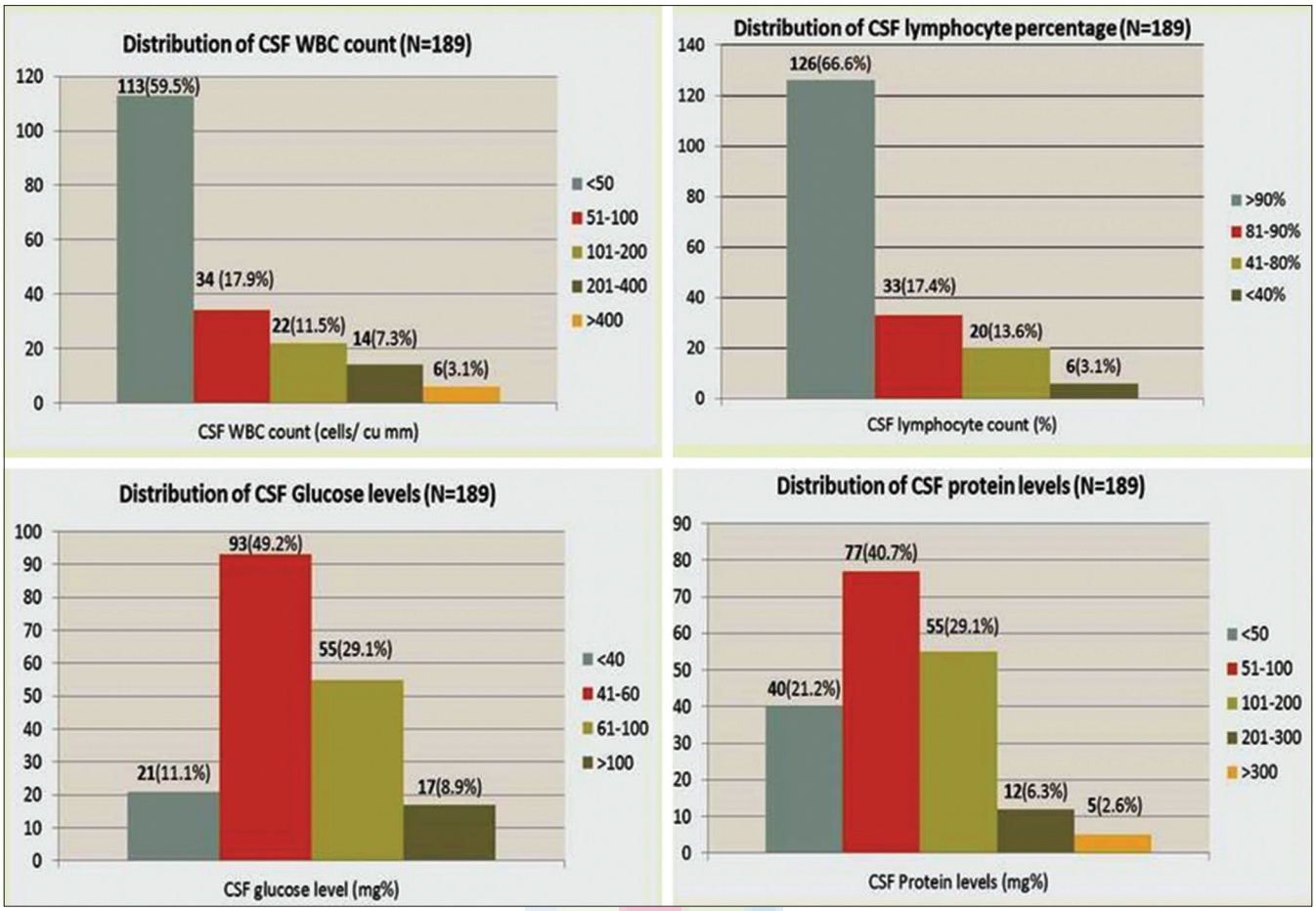

Figure 1: Details of the cerebrospinal fluid analysis

Table 2: CSF findings and correlation with eschar

	Eschar present (*N*=52)	Eschar absent (*N*=137)	95% Confidence Interval	
CSF WBC count (cells/cumm)	87.6 (123.0)	78.4 (120.7)	−30.1	48.6
CSF protein (mg %)	114.1 (108.3)	103.1 (68.6)	−21.5	43.4
CSF sugar (mg %)	59.4 (19.3)	72.8 (97.4)	−40.6	13.7

Mean (SD). WBC - White blood cell count, SD - Standard deviation, CSF - Cerebrospinal fluid

focal mononuclear cell exudate in the leptomeninges and the presence of typhus nodules (clusters of microglial cells) that are distributed throughout the brain substance.[3] Other CNS complications of scrub typhus include seizures, opso-myoclonus, acute disseminated encephalomyelitis, transient Parkinsonism, acute transverse myelitis and coma.[5-8] Cranial nerve deficits have been reported in up to 25% of patients, with the adbucens nerve being most commonly involved.[9] Trigeminal neuralgia, acute sensori-neural hearing loss and facial palsy have also been reported.[10-12] The reported complications of the peripheral nervous system include mononeuritis multiplex, brachial plexus neuropathy, polyneuropathy and Guillain–Barre syndrome.[13-15]

A pathognomonic eschar is a typical feature of scrub typhus and is of a high diagnostic value. An eschar was documented in 27.6% of our patients. The presence of an eschar is a highly variable finding, and the incidence varies from 10% to 92% of patients, with higher values being reported from the Orient. The dark skin of the Indian patients probably prevents the early identification of the eschars.[16] The mean duration of symptoms of 9.3 ± 4.8 days in our study is similar to that reported by Viswanathan *et al.* from the same geographic location.[9] The complete blood count (CBC) profile of patients with aseptic meningitis in this study was similar to the CBC profile of all patients with scrub typhus reported by Chrispal *et al*. and Kim *et al*.[2,16]

Scrub typhus commonly involves multiple organ systems, and more so in severe infection. We studied the involvement of other organ systems to assess the disease severity associated with CNS involvement. The incidence of pulmonary (19.7%) and renal involvement (18.6%) in our study was comparable to the incidences reported by Chrispal *et al.* (pulmonary: 24.9% and renal: 19.6%).[2] The incidence of cardiovascular involvement in the form of shock and

ionotropic requirements was also similar to the previously mentioned study (15% vs 14.8%).[2]

The mean CSF WBC count was 80 ± 120.7 cells/cu mm, which was similar to the value reported by Varghese *et al*. (83.2 cells/cu mm).[17] However, Pai *et al.* reported a much lower mean CSF WBC count of 16.3 cells/cu mm with a range of 0–110 cells/cu mm.[3] Mild to moderate pleocytosis in the range of 10–100 cells/cu mm were also reported by Berman *et al.* and Viswanathan *et al*.[9,18] We noticed a much wider range of CSF WBC count (5–900 cells/cu mm). The strength of our study is that our cohort is numerically the largest in the current literature of patients with meningitis/meningo-encephalitis due to scrub typhus. A CSF protein level of more than 100 mg% was seen in 38% of our patients. Our study showed a much wider range of protein levels (13–640 mg%) than that described by Boorugu *et al.* (14–360 mg%).[19] Markedly diminished CSF glucose values are generally seen in patients with bacterial meningitis. Our study has shown that 11% of patients with scrub typhus meningitis also have hypoglycorrhacchia. The comparison between other studies describing the CSF findings of scrub typhus meningitis/meningo-encephalitis is shown in Table 3.

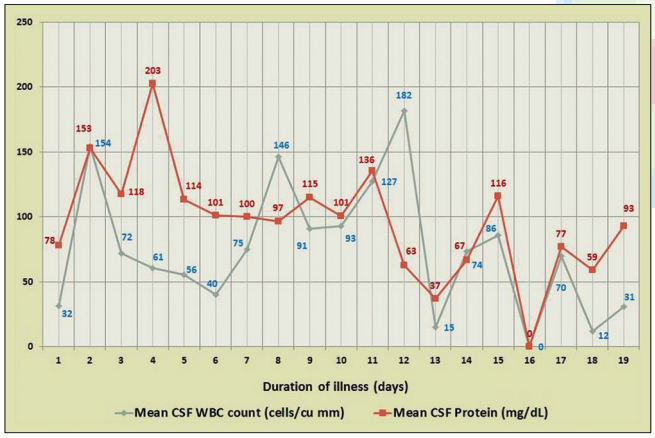

Figure 2: Temporal profile of CSF cellular and protein response in Scrub typhus

The case fatality rate in our study was 5.8%, which is comparable to the case fatality rates in recent studies on scrub typhus.[9] The rate was much higher (up to 30%) in studies performed before 2005.[20] Greater awareness of this re-emerging infection, and early recognition and empiric administration of doxycycline early in the course of the disease have probably contributed to the decreasing trend in mortality rates. Concerns remain over the concentrations of doxycycline in the CSF after oral administration. Intravenous administration of doxycycline or a higher oral dose may help in achieving higher CSF levels but this remains to be proven.

Our study was not without limitations. CSF analysis was not performed in some patients with scrub typhus and neck stiffness because of severe thrombocytopenia or coagulopathy and hence these patients could not be included in the analysis.

Conclusion

In endemic areas, scrub typhus should be considered one of the differentials of aseptic meningitis. CSF analysis in scrub typhus usually shows modest elevation in the WBC count with lymphocyte predominance, a moderately elevated protein level or a normal to low sugar level, and should be differentiated from other CNS infections.

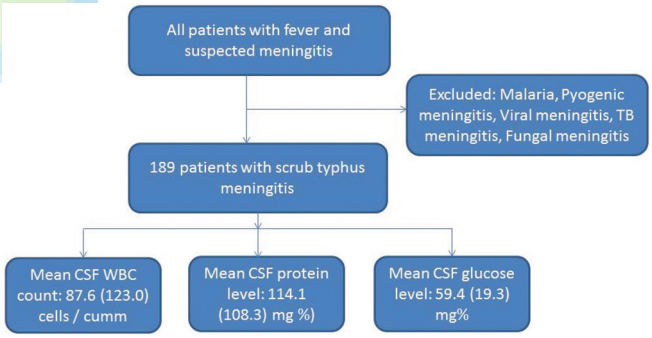

Figure 3: Flow chart of patients with scrub typhus meningitis

Table 3: Comparison of CSF analysis of meningitis due to scrub typhus with other studies

	Our study	Pai *et al*	Boorugu *et al*	Stalin *et al*	Varghese *et al*
Place	South India	Korea	South India	South India	South India
No. of patients	189	25	39	17	16
Mean CSF TC (cells/cumm)	80±120.7		47.3		83±83
Range	5-900	0-110	2-450	7-387	
Mean lymphocyte %	87.6		85.3		83±12.5
Range	12-100	11-80	30-100	68-100	
Mean Glucose (mg/dL)	105.9±80.9		67.6		81±44.5
Range	25-350	47-84	35-209	34-160	
Mean protein (mg/dL)	69.4±89.6		90.6		107±66.7
Range	13-640	10-110	14-360	32-340	

CSF - Cerebrospinal fluid

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How to cite this article: Abhilash KP, Gunasekaran K, Mitra S, Patole S, Sathyendra S, Jasmine S, *et al*. Scrub typhus meningitis: An under-recognized cause of aseptic meningitis in India. Neurol India 2015;63:209-14.

Source of Support: Nil, **Conflict of Interest:** None declared.