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

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ABSTRACT

Objectives: The involvement of the central nervous system in the form of meningitis or meningoencephalitis is common in scrub typhus and is an important differential diagnosis of other lymphocytic meningitis like tuberculous meningitis (TBM). The aim of this study was to identify the clinical and laboratory parameters that may be helpful in differentiating scrub typhus meningitis from TBM.

Patients and methods: We compared of the clinical and laboratory features of 57 patients admitted with scrub typhus meningitis or TBM during a 3-year period. Patients who had abnormal cerebrospinal fluid (CSF) and positive scrub typhus enzyme-linked immunosorbent assay serology (n = 28) were included in the scrub typhus meningitis group, while the TBM group included those who satisfied the consensus diagnostic criteria of TBM (n = 29).

Results: Compared with the TBM group, the mean duration of symptoms was less in patients with scrub typhus meningitis, who also had a lower magnitude of neurological deficits, such as altered mental status and cranial nerve and motor deficits. Patients with scrub typhus meningitis had a lower CSF white blood-cell count (WBC) than the TBM group (130.8 ± 213 195 ± 175 cells/mm^3, P = 0.002), lower CSF protein elevation (125 ± 120 *vs.* 195.2 ± 108.2 mg/dl, P = 0.002), and higher CSF sugar (70.1 ± 32.4 *vs.* 48.7 ± 23.4 mg/dl, P = 0.006). Features predictive of the diagnosis of scrub typhus meningitis included the absence of neurological impairment at presentation, blood serum glutamic-oxaloacetic transaminase > 40 international units (IU)/L, serum glutamic-pyruvic transaminase > 60 IU/L, total blood leukocyte count > 10,000/mm^3, CSF protein < 100 mg/dl, CSF sugar > 50 mg/dl, CSF WBC < 100 cells/mm^3. All patients with scrub typhus meningitis recovered completely following doxycycline therapy

Conclusions: This study suggests that, clinical features, including duration of fever, neurological deficits at presentation and laboratory parameters such as CSF pleocytosis,CSF protein elevation, CSF sugar levels and liver enzyme values are helpful in differentiating scrub typhus meningitis from tuberculous meningits. These features with scrub IgM serology may be helpful in identifying patients with scrub meningitis and in avoiding prolonged empirical antituberculous therapy in cases of lymphocytic meningitis.

1. Introduction

Scrub typhus is a vector borne rickettsial infection caused by *Orientia tsutsugamushi* and is commonly observed in terrains of the tsutsugamushi triangle, a geographical region of South and East Asia, including the Indian sub-continent and the Southwest Pacific. [1–3] The unique propensity of *O. tsutsugamushi* involving vascular endothelial cells results in multiple organ dysfunctions in scrub typhus. Scrub typhus involves both the central (CNS) and peripheral nervous systems. The CNS complications include meningitis, encephalitis, infarction, cerebellitis, hemorrhages, and demyelination. [4–6] The complications of the peripheral nervous system include mononeuritis multiplex, brachial plexus neuropathy, polyneuropathy, and Guillain Barre syndrome. [7–9] The CNS involvement is often a prominent clinical manifestation, and meningitis or meningoencephalitis occurs in 12–26% of the affected patients. [4,10] Scrub typhus meningitis is an important cause of meningitis in endemic areas. [11] However, it remains an unclear entity, and clinical features differentiating meningitis due to scrub typhus

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from other forms of meningitis are still lacking. In areas where both scrub typhus and tuberculosis are endemic, tuberculous meningitis (TBM) forms the closest and the most important differential diagnosis because both cause lymphocytic meningitis. The aim of this study was thus to identify the clinical and laboratory parameters that may be helpful in differentiating scrub typhus meningitis from common TBM.

2. Materials and methods

All patients aged 15 years or above who were hospitalized with a diagnosis of scrub typhus meningitis and TBM over a 3-year period were included in the study. The diagnosis of scrub typhus was confirmed by serum IgM enzyme-linked immunosorbent assay (ELISA; Scrub typhus Detect IgM ELISA, InBios India, detecting IgM antibodies to *O. tsutsugamushi* derived recombinant antigen). Meningitis was suspected and cerebrospinal fluid (CSF) analysis was performed if a patient had one or more of the following clinical features: Headache, nausea/vomiting, seizures, altered sensorium, or neck rigidity. In addition to CSF protein, sugar, and cell counts, the centrifuged deposit was subjected to the Grams, Ziehl-Neilsen, and India ink staining techniques to identify cell wall characteristics of bacteria and help identify *Mycobacteria* and *Cryptococcus* species. 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, were defined as scrub typhus meningitis cases. Patients hospitalized during the same period with a diagnosis of TBM were included as controls. We used the TBM consensus diagnostic criteria as previously reported by Marais et al. [12] Both definite and probable patients with TBM were included. The clinical and laboratory features of patients with scrub typhus meningitis and TBM were compared.

Statistical analysis was performed using the SPSS software for windows. Descriptive data were represented by the mean (standard deviation [SD]) or median (range). The chi-square test was used to compare dichotomous variables and Mann-Whitney test was used for continuous variables. Logistic regression analysis was performed after a univariate and multivariate analysis to predict the diagnosis of scrub typhus meningitis. A p-value < 0.05 was considered statistically significant.

3. Results

During the study period, there were 28 cases of scrub typhus meningitis. Of those, 14 were male patients and 14 were female patients. The most common presenting complaints were fever (100%), headache (82%), vomiting (71%) and seizures (32%). Pathognomonic eschar was found only in seven patients (25%). Three patients had papilledema, and one of those also had lateral rectus palsy.

The control group consisted of 29 patients (13 males and 16 females) diagnosed with TBM. Of those, 13 had definite TBM (positive CSF polymerase chain reaction [PCR] for tuberculosis) and 16 had probable TBM. Most common presenting complaints were fever (90%), headache (65%), seizures (48%) and altered mental status (62%). Five patients had papilledema, three had other cranial nerve deficits, and two had hemiparesis. The clinical and laboratory features of the cases and controls are presented in Table 1.

The duration of the fever prior to the presentation was longer in the TBM group than in the scrub typhus group (14.9 ± 19.6 days *vs.* 8.8 ± 3.4 days, p = 0.11). The patients with scrub typhus were less likely to present with seizures and altered mental status compared with patients with TBM. Focal deficits were more common in the TBM group.

The most notable laboratory findings on admission were a higher degree of elevation of liver enzymes in the scrub typhus meningitis group, while most of the TBM group had near normal values. Serum glutamic pyruvic transaminase (SGPT) levels > 65 international units (IU) and serum glutamic oxaloacetic transaminase (SGOT) > 40 IU/L were observed in 79% and 89% of patients with scrub typhus meningitis, respectively. Leukocytosis was significantly higher in the scrub typhus meningitis group (13,260 ± 4,626.5 *vs.* 9220 ± 4,014.3; p = 0.002). The blood hemoglobin level and erythrocyte sedimentation rate (ESR) did not differ significantly between the two groups.

Table 1
patient characteristics, laboratory features and CSF analysis.

Parameter	Scrub typhus meningitis n = 28 (%)	Tuberculous meningitis N = 29 (%)	P value
Age	40.2 ± 17.6	47.1 ± 18	0.145
Duration of fever	8.8 ± 3.4	15 ± 9.7	0.04
Headache	23 (82)	19 (65.5)	0.15
Seizure	9(32)	14(48.3)	0.21
Altered mental status	8(28.6)	18(62)	0.01
Neck stiffness	14(50)	21(72)	0.08
CSF-TC(cells/cumm)	130.8 ± 213	195 ± 175	0.002
CSF-Protein (mg/dl)	125 ± 120	195.2 ± 108.2	0.002
CSF Sugar (mg/dl)	70.1 ± 32.4	48.7 ± 23.4	0.006
Hb (gm/dl)	12.8 ± 1.72	12.3 ± 1.8	0.194
ESR(mm/hr)	32.6 ± 15.7	39.6 ± 25.1	0.227
WBC count (cells/cumm)	13260.7 ± 4626.5	9220 ± 4014.3	0.002
SGOT (IU/L)	135 ± 97.7	39.6 ± 50.8	< 0.001
SGPT (IU/L)	150 +112.7	46.5 ± 27.4	< 0.001
ALP (IU/L)	204.7 ± 95.7	140.7 ± 136.2	0.012
Total bilirubin (mg/dl)	1.64 ± 2.45	1.16 ± 1.69	0.89

In contrast, the CSF findings were markedly different between the two groups. The scrub typhus group had a lower CSF pleocytosis and a lesser degree of protein elevation. More than the 2/3rd of the scrub typhus cases had a CSF cell count up to 100 cells/mm^3, while only 14.3% of the patients had counts exceeding 200 cells/mm^3. In the TBM group, nearly half of the patients had cell counts between 100 and 200 cells/mm^3 (Fig. 1). Both groups had CSF lymphocytic pleocytosis, with a mean lymphocytic level of 99% in the scrub typhus group and 96% in the TBM group. The mean CSF cell count was significantly higher in the TBM group. Approximately 50% of the scrub typhus cases had a CSF protein level below 100 mg/dl, whereas 61% of the TBM group had CSF protein between 100–200 mg/dl (Fig. 2). The mean CSF protein level was significantly higher in the TBM group. A CSF sugar level below 50 mg/dl was observed in 48% of the patients with TBM and 14% of the patients with scrub typhus (Fig. 3).

A comparison of clinical and laboratory features including 3 groups,

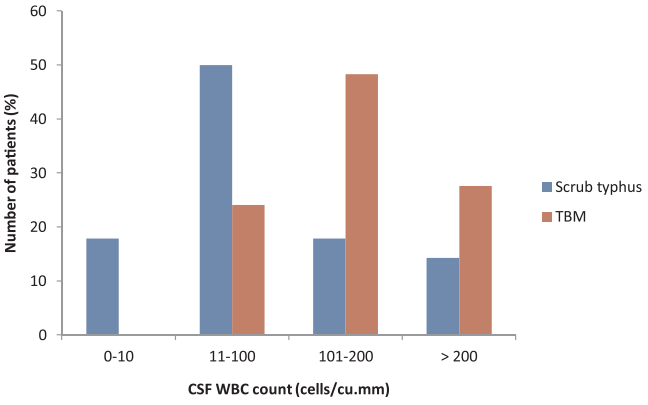

Fig. 1. Distribution of CSF WBC count.
Comparison of CSF WBC count in patients with scrub typhus meningitis and tuberculous meningitis (p value 0.002)

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