The clinical biochemical and hematological profile of scrub typhus meningoencephalitis

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ABSTRACT

Background: Scrub typhus is a zoonotic infectious disease caused by the Gram-negative coccobacillus Orientia tsutsugamushi. Meningoencephalitis occurs in two-thirds of all the infected cases. Aims and Objectives: The study of these cases was conducted to study the clinical, biochemical, and hematological features of scrub typhus meningoencephalitis. Materials and Methods: We included 12 patients who were admitted in the General Medicine Ward of Medical College and Hospital, Kolkata, between May 2021 and July 2022. The serum scrub typhus immunoglobulin M (IgM) test was used to diagnose the cases after ruling out dengue, malaria, leptospirosis, bacterial, tubercular, and viral meningoencephalitis. Results: A triad of fever, altered sensorium, and meningeal signs were present in all of the cases. 2 patients had seizures, 1 patient had lateral rectus palsy, 1 patient had a generalized maculopapular rash, and eschar was seen in only 2 cases. The most common laboratory abnormalities were hyponatremia, anemia, and transaminitis (each 83.33%). 8 cases (66.7%) had a combination of anemia, hyponatremia, and transaminitis. Cerebrospinal fluid abnormalities included protein elevation (75%) and lymphocytic pleocytosis (83.33%). Scrub typhus IgM was positive in all of them. All the cases showed excellent response to doxycycline. Conclusion: A high degree of clinical suspicion is required to diagnose scrub typhus meningoencephalitis. The eschar is detected in very few cases and it may be difficult to recognize the same among the dark-skinned Indian population. However, as per our study, any case of meningoencephalitis with a combination of anemia, hyponatremia, and deranged liver function tests should always raise the possibility of the aforementioned disease and doxycycline therapy must be started promptly.

Key words: Scrub typhus; Meningoencephalitis; Hyponatremia; Doxycycline

INTRODUCTION

Scrub typhus is a zoonotic infection caused by Orientia tsutsugamushi, an intracellular rickettsia. It is transmitted by the bite of the larvae of the trombiculid mite. It is endemic to the tsutsugamushi triangle, comprising parts of South-East Asia and the South-West Pacific. Several states of India, including West Bengal, are a part of this triangle.¹ With a case fatality rate of 30% (if left untreated), it is one of the most important re-emerging infections in India.² A large number of cases are reported from West Bengal every year, from the rainy season up to the winter months, coinciding with the time when the mite lays its eggs. The disease can involve a number of organs and thus can have myriad presentations. The most pathognomonic feature of the disease is an eschar, which is found in the “hidden” areas of the body such as the groin, axilla, neck, and over the genitalia. Eschars are, however, often missed in the dark-skinned Indian population and are also not found in a significant proportion of cases.³ The neurological complications reported in the disease include aseptic meningitis, meningoencephalitis, cerebellitis, myelitis, cerebral hemorrhage, acute disseminated encephalomyelitis, and cerebral infarction. However, the most common neurological complication reported thus...
far is meningoencephalitis. For any case presenting with meningoencephalitis, several etiologies such as pyogenic, tubercular, viral, and scrub typhus, can be considered. Owing to overlapping clinical features and rare occurrence of eschars among these patients, it is often difficult to identify such patients. Hence, it is necessary to identify biochemical, hematological, and cerebrospinal fluid (CSF) characteristics that are predictive of scrub typhus meningoencephalitis, so that prompt therapy can be initiated.

In this case series, we have reported 12 cases of scrub typhus meningoencephalitis admitted in our General Medicine Ward at Medical College and Hospital, Kolkata.

Aims and objectives
The primary aim of the case series was to study the clinical, biochemical, and hematological features of scrub typhus meningoencephalitis.

MATERIALS AND METHODS
This was a hospital-based prospective observational study conducted in the Department of General Medicine at Medical College and Hospital, Kolkata, between May 2021 and July 2022.

Inclusion criteria
All patients above the age of 12 years presenting with fever, headache, altered sensorium, and signs of meningeal irritation with positive scrub typhus immunoglobulin M (IgM) antibodies (optical density value [ODV] >0.5).

Exclusion criteria
Patients with central nervous system disease not attributable to scrub typhus (pyogenic, viral, tubercular meningoencephalitis).

Meningoencephalitis was clinically defined by the presence of headache, and/or nuchal rigidity, with either altered sensorium or focal neurological deficits.

Diagnosis was established with positive serum scrub typhus IgM antibody test (with an ODV of >0.5).

We included 12 patients who were admitted in the General Medicine Ward of Medical College and Hospital, Kolkata, with acute meningoencephalitis syndrome and a positive scrub typhus IgM antibody test.

All of the patients were admitted with fever, headache, and altered sensorium (acute encephalitis syndrome) along with signs of meningeal irritation.

Dengue, malaria, leptospirosis, bacterial, tubercular, and viral meningoencephalitis were ruled out.

Complete hemogram, electrolyte assays (Na, K), kidney function tests (urea, creatinine), liver function tests (SGOT, SGPT, bilirubin, and PT/include prothrombin time), and CSF studies were done.

Data were obtained and response to therapy with doxycycline was noted.

RESULTS
The mean age of study group was 34.25. There were 7 male and 5 female patients. A triad of fever, altered sensorium, and meningeal signs were present in 100% of cases (Table 1).

Fever, headache, altered sensorium, and neck rigidity were seen in all of the cases. 2 patients had seizures, 1 patient had lateral rectus palsy (Figure 1), 1 patient had a generalized maculopapular (Figure 2) rash, and eschar was seen in only 2 cases (Figure 3). The most common
laboratory abnormalities were hyponatremia, anemia, and transaminitis (each 83.33%) and leukocytosis (33.3%). Only 1 patient was reported to have AKI. C-reactive protein was elevated in all the cases. Thrombocytopenia was seen in 3 cases (27.5%). Pancytopenia was seen in 2 cases. 8 cases (66.7%) had a combination of anemia, hyponatremia, and transaminitis. CSF was abnormal in all cases with protein elevation (75%) and lymphocytic pleocytosis (83.33%). Scrub typhus IgM was positive in all of them with an ODV >0.5. All the cases showed excellent response to doxycycline and recovered without any deficits.

DISCUSSION

Acute meningoencephalitis is a common clinical syndrome plaguing the Indian subcontinent, particularly in the rainy season. According to a study conducted in North Bengal Medical College on acute encephalitis syndrome, scrub typhus was found to be responsible for 10.05% cases, making it one of the main etiological agents alongside Japanese encephalitis virus and Dengue virus. In a 4-year surveillance study by Ravi et al., 10,107 patients with acute encephalitis syndrome across Uttar Pradesh, West Bengal, and Assam were studied and scrub typhus was found to be the second most common cause for the syndrome (JE virus being the most common cause), accounting for 18.5% of the cases.6 Scrub typhus has an excellent response rate to doxycycline if introduced timely. Hence, it is of paramount importance to know the clinical and laboratory parameters suggestive of scrub typhus, so that empirical therapy can be started before serological confirmation.

In the present study, males accounted for the majority, probably because they were more involved with outdoor activity that exposed them to chigger bites. The triad of headache, fever, neck rigidity, and altered sensorium were present in all the cases. The mean duration of fever was found to be 5±1.044 days. Seizures were seen in 2 cases (16.7%) of the cases (Table 1). As per other studies, seizures are seen in 22–50% of cases with neurological involvement.5,7,8 Cranial nerve involvement, particularly unilateral or bilateral sixth nerve palsies, is sparsely reported. In our study, only one case had developed a right lateral rectus palsy that improved with antibiotic treatment. The pathognomonic eschar was noted in 2 cases (16.7%) only. Several studies have concluded that patients residing in areas endemic to scrub typhus often lack eschars. One patient presented with generalized maculopapular rash. As per studies, maculopapular rashes can be observed in 25–50% of cases.10

In our study, anemia was seen in 10 cases (83.33%), leukocytosis in 4 cases (33.3%), and thrombocytopenia was seen in 3 cases (25%). The mean Hb value was 10.3±2.33 mg/dL (Table 2). In a large series on scrub typhus conducted in North India, Sharma et al. had reported anemia in 54% of cases, leukopenia in 15%, and thrombocytopenia in 90% of cases.11 In our study, pancytopenia was observed in 2 cases and they were diagnosed with hemophagocytic lymphohistiocytosis (HLH). Both of them improved with doxycycline. HLH is often reported in scrub typhus.12

The most common electrolyte abnormality in our study was hyponatremia (83.3%). The mean sodium value in the study was found to be 129.83±6.41 mEQ/L (Table 3). It has been reported in varying frequencies from several studies, both in adult and pediatric populations.13-15 The reason behind hyponatremia may be multiple including sodium loss, cellular sodium influx due to decreased sodium-potassium ATPase activity, increased level of anti-diuretic hormone, and osmo-receptor resetting.

Hypokalemia was seen in 33.3% of cases. The mean potassium in our study was found to be 3.74±0.68 mEQ/L. In a study encompassing 502 patients of scrub typhus, Sedhain and Bhattarai had reported that only 1.34% of them had hypokalemia.14

Only one patient developed AKI in our study population.

Transaminitis was observed in 10 out of 12 cases (83.33%). 5 patients showed predominant SGOT elevation while the other 5 showed predominant SGPT elevation (mean value of SGOT=507.16 ± 1000.53 units/L, SGPT=273.41 ± 613.68 units/L) (Table 3). Previous studies have reported that hepatic dysfunction in patients with scrub typhus was found to be a hepatocellular-patterned abnormality. The possible mechanisms could be direct cytopathic liver injury and hepatic sinusoidal endothelial vasculitis.16
Direct hyperbilirubinemia was observed in 2 cases and prolonged PT was seen in 4 cases (33.3%) (Table 3).

CSF studies were abnormal in all the cases. CSF pleocytosis (cell count >5 cells/mm\(^3\)) was observed in all 12 cases, with 2 of them showing neutrophilic predominance while the remaining showed lymphocytic predominance (83.3%). CSF protein was elevated in 9 cases (25%) while CSF glucose values were mostly normal. The mean CSF cell count was 66.67±100.48 cells/mm\(^3\), mean CSF protein was 65.75±35.60 mg/dL, and mean CSF glucose was 73.58±19.90 mg/dL (Table 4). These findings are concordant with other studies.\(^\text{15,17}\)

The CSF pleocytosis, being predominantly lymphocytic along with raised CSF protein levels, can often lead to a presumptive diagnosis of tubercular or viral meningoencephalitis. Antitubercular therapies may often be initiated for such cases. The inherent hepatotoxicity of such drugs coupled with the hepatic inflammation caused by scrub typhus and could precipitate a fatal episode of acute liver failure. Thus, initiating doxycycline (instead of ATT) empirically is a better option in such scenarios.

In 2020, Alam et al. had reported that fever for >8 days, pneumonia, absence of petechiae, CSF protein >1000 mg/L, and serum glutamic oxaloacetic transaminase >100 IU/L as independent “predictors” of scrub typhus meningoencephalitis in children.\(^\text{18}\)

Venkatesan and Eswaradass concluded in their study that meningoencephalitis with altered LFT should raise the suspicion of scrub typhus meningoencephalitis.\(^\text{19}\)

In our study, we found that a combination of anemia, hyponatremia, and transaminitis was present in 66.7% of the cases.

Thus, any patient of acute meningoencephalitis with a combination of anemia, hyponatremia, and transaminitis must raise the suspicion of scrub typhus and therapy with doxycycline must be started promptly for such cases.

**CONCLUSION**

Meningoencephalitis is a common manifestation of scrub typhus and diagnosis requires high degree of clinical suspicion which if diagnosed early and specific treatment started, patients usually recover completely with few complications.
Table 4: CSF features of the 12 case subjects

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<th>Case no. (CN)</th>
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<th>CSF cell type (%)</th>
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<th>CSF protein (mg/dl)</th>
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CSF: Cerebrospinal fluid

REFERENCES


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