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Research Article

A Study of Clinico-radiological, CSF Profile and Outcome of Scrub Typhus Meningoencephalitis with Special Reference to Atypical Presentation

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ABSTRACT

Background: Scrub typhus is an endemic disease, which is caused by Orientia tsutsugamushi. Scrub typhus affects a region known as "the tsutsugamushi triangle", which starts from the northern part of Japan and extends to the southern part of Northern Australia, northern part of Russia, and Pakistan. The present study focued to generate evidence regarding clinical manifestation and treatment outcome of the scrub typhus meningoencephalitis cases admitted in a tertiary care centre of Burdwan, West Bengal.

Materials & Methods: The cross-sectional observational study was done at inpatient department of General Medicine, Burdwan Medical College & Hospital, Burdwan, West Bengal. The duration of study was 18 months. Diagnosed patients of scrub typhus meningoencephalitis, attending inpatient (IPD) department of General Medicine were included in study population. Calculated final sample size was 68. Liver function test, renal function test, coagulation profile, CSF analysis, NCCT brain, MRI brain was done.

Results: Prevalence of serious scrub typhus infection was 68.6%. Nearly 44.3% study subjects were within 18-36 years age group; majority were male (64.3%). 70% had shown Eschar formation. 44.3% had comorbidities. Nearly 43% study subjects presented with pallor, 38% presented with icterus, 27.6% with hypotension, 21% with hepatomegaly, 18.4% with splenomegaly and 22% with neck rigidity. Nearly 57.1% study subjects had bleeding disorder, 37.1% with hepatitis, 25.7% with acute kidney injury and 22.9% with meningitis. Age and Eschar formation had significant associations with disease severity of study subjects. Coagulation profile (platelet, INR, D-dimer, APTT), serum urea, creatinine, liver function (bilirubin, SGOT, SGPT, albumin) and total count of WBC, Hemoglobin, CRP and serum ferritin were also significantly associated with treatment outcome.

Conclusion: Atypical presentations in scrub typhus were common and they were needed to be treated early to reduce morbidity & mortality burden of the disease.

Keywords: Scrub typhus, meningoencephalitis, Coagulation profile, MRI.

INTRODUCTION

Scrub typhus is a zoonosis that results from Orientia tsutsugamushi infection and is known to be endemic to the "tsutsugamushi triangle" that extends from northern Japan to northern Australia and from far-eastern Russia to Pakistan. The disease has resurfaced in India after years of inactivity and has been documented in several states of India, such as West Bengal, Himachal Pradesh, Tamil Nadu, Kerala, Maharashtra, Karnataka, Rajasthan, and Jammu & Kashmir. A diagnostic tool used for detection is the enzyme-linked immunosorbent assay (ELISA) for IgM antibodies to O. tsutsugamushi.[1-3]

It is transmitted by the bite of infected larval trombiculid mites (chiggers) belonging to the Leptotrombidium genus. Following inoculation, O. tsutsugamushi invades endothelial cells and phagocytes, producing a systemic vasculitic process that can affect multiple organs. The clinical spectrum ranges from a self-limiting febrile illness to severe disease with multiorgan dysfunction and mortality rates reaching 35–50% if diagnosis and treatment are delayed6.[4-6]

The most common initial symptom is acute fever and may be accompanied by headache, myalgia, cough, breathlessness, nausea, and vomiting. An eschar, although considered characteristic, is observed in only a variable proportion of cases. Severe complications include acute respiratory distress syndrome, hepatitis, acute kidney injury, myocarditis, shock, and central nervous system involvement such as meningoencephalitis.[7] The diagnosis is often challenging because of the non-specific clinical presentation and overlap with other tropical infections. Laboratory abnormalities are also variable;

thrombocytopenia is common, while mild transaminitis is among the most consistent findings, reported in the majority of patients. Renal dysfunction has also been documented with varying frequency10. [8-10] Traditional diagnostic methods such as the Weil–Felix test have poor sensitivity and specificity, whereas IgM ELISA and immunofluorescence assay (IFA) remain the preferred diagnostic modalities.[11,12]

Scrub typhus is characterized pathologically by disseminated vasculitis and perivasculitis. Infection induces a type-1 immune response with increased levels of interferon-α, interleukin-18, and interleukin-15, leading to endothelial injury and vascular leakage. These changes may result in shock, hepatic and renal dysfunction, pulmonary edema, and meningoencephalitis. Severe infection can also trigger coagulation abnormalities ranging from mild thrombocytopenia to disseminated intravascular coagulation (DIC), contributing to both thrombotic and hemorrhagic complications and ultimately multiorgan dysfunction.[13] Neurological manifestations of scrub typhus are increasingly recognized. Viswanathan et al.[14] conducted a study that showed almost one fourth scrub typhus patients developed meningitis. Cerebrospinal fluid findings typically showed lymphocytic pleocytosis and elevated protein levels, often mimicking tuberculous meningitis. The authors highlighted the usefulness of CSF adenosine deaminase levels and scrub typhus IgM testing in differentiating scrub meningitis from tuberculosis and avoiding unnecessary empirical antitubercular therapy.

Despite the growing recognition of neurological involvement, data regarding the clinico-radiological profile, CSF characteristics, and outcomes of scrub typhus meningoencephalitis remain limited, particularly in West Bengal. Furthermore, no such study has been reported from Purba Burdwan district. The study was conducted to generate evidence on the clinico-radiological features, cerebrospinal fluid (CSF) profile, treatment outcomes, and atypical presentations of patients with scrub typhus meningoencephalitis admitted to a tertiary care centre in West Bengal.

MATERIALS AND METHODS:

The cross-sectional observational study was conducted in the Department of General Medicine, Burdwan Medical College and Hospital (BMCH), West Bengal, for over 18 months (June 2023 to December 2024). The study included patients >12 years of age admitted with scrub typhus meningoencephalitis, defined as fever with or without eschar, confirmed by serological or molecular testing for Orientia tsutsugamushi, along with neurological manifestations such as altered sensorium, seizures, or nausea/vomiting. Patients who did not provide informed consent, had negative scrub typhus reports, concomitant diagnoses of malaria, dengue, tuberculosis, leptospirosis, leukemia, bacterial meningitis, chronic liver or kidney disease, immunocompromised states, or acute respiratory distress syndrome were excluded.

The sample size calculation was done using the prevalence of scrub typhus meningoencephalitis reported by Jamil et al. [15] (13.2%), applying the formula $n = Z^2p(1-p)/d^2$ with a 95% confidence interval and 8% absolute precision, yielding a minimum sample size of 68 participants.

The data for this study was gathered using pre-designed and pre-tested semi-structured schedule using interview technique, clinical assessment of patients, and clinical review of records where necessary. The demographic and clinical data collected included age, gender, educational status, socioeconomic status, comorbid conditions, presenting complaints, and vital signs. The laboratory tests done included complete blood counts, liver and renal function test, serum ferritin level, C-Reactive Protein (CRP), and prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (APTT), platelet count, and D-dimer level. Analysis of cerebrospinal fluid (CSF) was carried out in all the cases studied. The neuroimaging tests done included non-contrast computed tomography (NCCT) and Magnetic Resonance Imaging (MRI). Laboratory and radiological support were provided by the Departments of Pathology, Biochemistry, and Radiology, BMCH.

Scrub typhus was diagnosed based on a positive IgM ELISA result for *Orientia tsutsugamushi*. Acute kidney injury was identified according to the criteria established by the Acute Kidney Injury Network (AKIN), while acute hepatitis was defined as serum transaminase levels exceeding twice the upper limit of normal. Coagulopathy was identified by prolonged clotting parameters or clinical bleeding manifestations. Treatment outcomes were categorized as discharged, death, or left against medical advice (LAMA) and were verified from hospital records.

The study received ethical clearance from the Institutional Ethics Committee of Burdwan Medical College and Hospital, West Bengal (Memo No. BMC/IEC/2023/185). Prior written informed consent was obtained from all study participants or their legally authorized representatives before enrollment in the study. Participant confidentiality and privacy were maintained throughout the study.

Data were entered into Microsoft Excel and then subjected to statistical analysis using SPSS software version 23. The mean ± SD was used to represent continuous variables, while frequencies (%) were used to represent categorical variables. The relationship between the variables was determined by carrying out bivariate analysis that included the Chi-square test and unpaired t-test where necessary. A significance level of $p \leq 0.05$ was used.

RESULTS

Among the 68 patients, the mean age was 39.9 ± 13.6 years and majority of them were in the age group of 18–36 years (44.3%). Males constituted 64.3% of the study population. Most patients included in the study were from rural backgrounds (80.0%), had primary or middle-school education (72.8%), and belonged to the lower-middle socioeconomic class (40.0%). Eschar was identified in 70.0% of patients, while 44.3% had associated comorbidities. Patients presented after a mean illness duration of 6.7 ± 1.7 days.

Clinical Manifestations

Headache (95.0%), fever (88.0%), altered sensorium (77.0%), and nausea/vomiting (68.0%) were the most common presenting symptoms. Petechial rash and jaundice were observed in 47.0% and 38.0% of patients, respectively. Neck rigidity was the predominant neurological sign, present in 56.8% of cases. Other notable clinical findings included pallor, icterus, hypotension/shock, hepatomegaly, and splenomegaly.

Laboratory Findings

Patients demonstrated evidence of systemic inflammation, hepatic dysfunction, renal impairment, thrombocytopenia, and coagulopathy. Elevated inflammatory markers, including CRP and ferritin, were frequently observed. Liver function abnormalities were characterized by elevated bilirubin and transaminases, while renal dysfunction was reflected by increased serum urea and creatinine levels. Coagulation abnormalities included thrombocytopenia, prolonged INR and APTT, and elevated D-dimer levels.

Neuroimaging Findings

Magnetic resonance imaging revealed cerebral edema in 79.0% of patients and hyperintense lesions involving the thalamic and basal ganglia regions in 68.0%. Leptomeningeal enhancement was observed in 16.0% of cases. On non-contrast CT brain, diffuse cerebral edema was the most common abnormality, whereas nearly one-third of patients had no significant CT abnormalities.

Cerebrospinal Fluid Profile

CSF analysis demonstrated a characteristic pattern of lymphocytic pleocytosis with elevated protein levels and mildly reduced glucose levels. The majority of patients exhibited CSF cell counts between 50 and 100 cells/mm³ with predominant lymphocytic infiltration. Elevated CSF protein and borderline raised opening pressure were common findings.

Atypical Manifestations

Bleeding manifestations were the most frequent atypical presentation, occurring in more than half of the patients. Other atypical manifestations included hepatitis, pneumonia, acute kidney injury, meningitis, acute respiratory distress syndrome, and ptosis. Altered sensorium remained the most common neurological manifestation throughout the disease course.

Treatment Outcomes

A favorable outcome was achieved in 48 patients (70.6%), who were discharged in stable condition. Twenty patients (29.4%) had unfavorable outcomes, including 15 patients who left against medical advice and 5 in-hospital deaths, resulting in an overall mortality rate of 7.3%.

Factors Associated with Outcome

Age (p=0.004) and eschar formation (p=0.013) were the only baseline characteristics significantly associated with treatment outcome. (Table 1)

Patients with unfavorable outcomes demonstrated significantly greater systemic inflammation, with higher total leukocyte count, CRP, and ferritin levels (all p=0.000). Markers of hepatic dysfunction, including bilirubin, SGOT, SGPT, and albumin, were significantly associated with adverse outcomes (p values being 0.001, 0.003, 0.008, and 0.026, respectively). Similarly, renal dysfunction markers, namely serum urea and creatinine, were significantly elevated among patients with unfavorable outcomes (p=0.005 and p=0.000, respectively). Coagulation abnormalities were strongly associated with poor prognosis. Lower platelet counts, elevated INR, prolonged APTT, and increased D-dimer levels were all significantly associated with unfavorable outcomes (p values being 0.000, 0.035, 0.000, and 0.000, respectively). Neurological severity at presentation, reflected by lower Glasgow Coma Scale scores, was also significantly associated with adverse outcomes (p=0.041). (Table 2)

Predictors of Atypical Presentation

Receiver operating characteristic analysis demonstrated excellent predictive performance of APTT for coagulopathic manifestations of scrub typhus meningoencephalitis (AUC=0.920, p=0.000). Serum SGOT showed moderate predictive value for hepatitis-related atypical presentations (AUC=0.659, p=0.034). (Figure 1, 2)

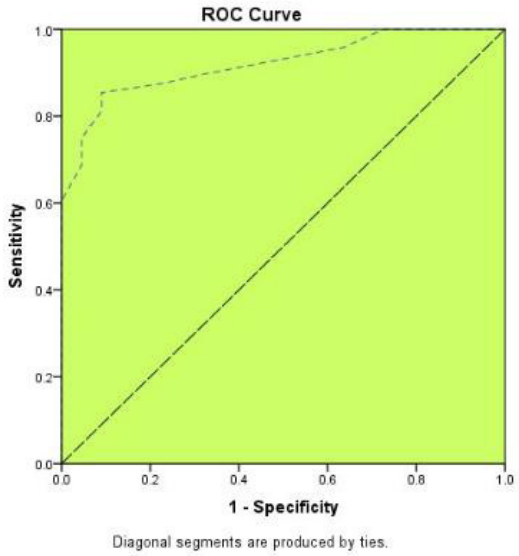

Figure 1: ROC curve analysis for APTT values to predict atypical presentation (coagulopathy) of scrub typhus meningoencephalitis cases (n=68)

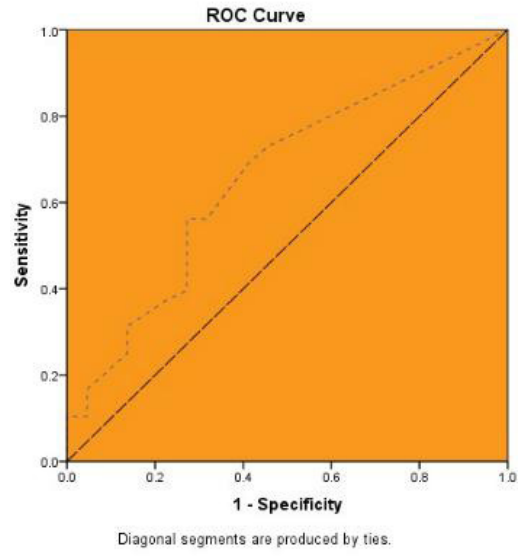

Figure 2: ROC curve analysis for serum SGOT level to predict atypical presentation (hepatitis) in scrub typhus meningoencephalitis cases (n=68)

Table 1: Association between background characteristics and treatment outcome

Background characteristics	*Total study subjects (N=68)*	*Unfavorable outcome (n=20)*	*Favorable outcome (n=48)*	*χ^2 value*	*DF*	*p-value*
Age (years)						
<18	4	3	1	13.219	3	**0.004**
18–36	31	14	17			
36–54	20	4	16			
>54	13	2	11			
Duration of illness (days)						
<5	10	3	7	3.538	2	0.171
5–7	36	14	22			
>7	22	4	18			
Religion						
Hindu	22	12	10	2.435	2	0.087
Muslim	29	9	20			
Others	17	8	9			
Gender						
Male	43	13	30	0.377	1	0.539
Female	25	9	16			
Residence						
Urban	13	4	9	0.066	1	0.797
Rural	55	18	37			
Co-morbidities						
Present	31	7	24	2.021	1	0.155
Absent	37	15	22			
Educational status						
Illiterate	11	2	9	6.233	3	0.101
Primary	25	10	15			
Middle school	24	9	15			
Secondary	8	3	5			
Eschar formation						
Present	47	10	37	6.111	1	**0.013**
Absent	21	11	10			

DISCUSSION

The present study was supposed to assess the spectrum of clinical profile among scrub typhus patients in a tertiary care centre of West Bengal, India. In the study, majority of the study subjects were within 18-36 years age group. Male predominance was evident. Significant portion of study subjects were either from middle class or lower-middle class. Most of the study subjects had primary and mid school level of education. Most of the patients were admitted for 5-7 days. Majority of them were found to have Eschar. Maximum patients had comorbidities. Majority of them had pallor, hypotension, icterus, hepatomegaly, splenomegaly, neck rigidity and cyanosis. Majority of study subjects were found to have fever, headache, nausea/vomiting, jaundice, petechial rash, black stool, epistaxis, altered sensorium. Significant abnormalities in liver function, kidney function, coagulation profile was detected. Overall rate of complications was considerably high among study subjects, pneumonia, hepatitis, meningitis, ARDS, acute kidney injury were the predominant forms. Case fatality rate was high among study subjects. Age and eschar formation were associated with treatment outcome. Total count of WBC, CRP, serum ferritin, renal function (urea, creatinine), liver function (bilirubin, SGOT, SGPT, INR) and coagulation profile (platelet, INR, APTT, D-dimer) were

Table 2: Association between biochemical characteristics and treatment outcome

Biochemical parameters	*Unfavorable, Mean (SD)*	*Favorable, Mean (SD)*	*t-value*	*p-value*
Hematological profile				
Total count of WBC (per dl)	6363.182 (1566.184)	10934.646 (3960.085)	-5.214	0.000
Hemoglobin (g/dl)	10.777 (1.605)	8.881 (1.989)	3.919	0.000
Ferritin (ng/ml)	367.227 (83.432)	527.50 (77.389)	-7.85	0.000
CRP	2.045 (0.933)	4.585 (2.172)	-5.25	0.000
Liver profile				
Bilirubin (mg/dl)	1.135 (0.507)	2.896 (1.976)	-3.609	0.001
SGOT (u/l)	62.091 (37.463)	193.729 (197.96)	-3.082	0.003
SGPT (u/l)	63.045 (40.563)	163.04 (167.84)	-2.748	0.008
Albumin (u/l)	4.250 (0.435)	3.829 (0.810)	2.284	0.026
Kidney profile				
Urea (mg/dl)	21.773 (5.622)	43.979 (35.909)	-2.905	0.005
Creatinine (mg/dl)	1.055 (0.153)	1.990 (1.147)	-3.792	0.000
Coagulation profile				
Platelet (per dl)	112967 (28698.67)	71678.47 (44892.87)	3.951	0.000
INR	1.618 (0.919)	2.202 (1.112)	-2.146	0.035
APTT (sec)	27.136 (2.474)	34.271 (3.723)	-8.181	0.000
D-dimer	1.00 (1.039)	5.060 (2.629)	-6.974	0.000
Level of consciousness				
GCS score	4.081 (1.086)	9.216 (1.026)	2.162	0.041

significantly associated with treatment outcome. ROC curve analysis showed that serum APTT and serum SGOT level could be used to predict coagulopathy and hepatitis (atypical presentations) among scrub typhus meningoencephalitis cases.

The global scenario regarding scrub typhus patients in tertiary care centre was somewhat similar but with wide variability. Several studies from Chennai, Gujrat, Manipur, Andaman, Nepal, Pakistan, Sri Lanka, Nigeria, Ethiopia did hint about the lack of care in such treatment facilities.[16,17] The current study showed that 29.4% study subjects were had unfavorable treatment outcome. Another study in India by Nowneet Kumar Bhat et al found mortality rate of 7.5%.[18]

Scrub typhus is a rickettsial infection prevalent in India. This is the reason we performed this study to assess the clinical and biochemical profiles of scrub typhus infections. Patients included in the study were relatively young with mean age of 39 years and were from rural background, which may be attributed to the higher involvement of younger people in farming activities in rural areas. Higher incidence of disease among males than females showed the importance of males in farming practices in Eastern India. These results are corroborated by many previous studies. Lakshmi RMMV et al reported the patients having age range of 20 to 50 years. [19] However, contrary to above study, Pathania M et al reported the prevalence of the disease among young adult population with age range of 20 to 40 years with female-to-male ratio being 2.8:1.[20] Another study by Zhang M et al reported that higher age groups with mean age of 54 years had increased prevalence of scrub typhus with female to male ratio of 1.08:1. [21] Study by Jayprakash V et al also reported that mean age was 45.7 $\pm$ 15 years with female to male ratio 1.68:1.[22]

The mean duration of fever among patients at presentation in our study was 6.7 days. Fever was high-grade, persistent, and responsive to antipyretic medication in most of the cases. Fever was accompanied by chills in 20 (38.5%) patients. According to Lakshmi RMMV et al, the majority of the cases (58.6%) showed fever for more than 7 days, and 10.3% had fever for 2 weeks or more.[19] Similarly, according to Pathania M et al, the mean duration of disease was 9.8 $\pm$ 4 days, which is similar to the findings in our study.[20] In the study of Zhang M et al, the mean duration of fever was 6.6 days, where 35.3% had continuous fever, 23.5% remittent, 34.3% irregular, and 6.9% unspecified. [21]

Other common complaints included headache in 95% cases, and nausea and vomiting in 68% of the cases. Eschar, which is described as a distinctive dark-colored necrotic cutaneous lesion, occurred in only 49 patients (70%). Most commonly, eschar was found on the thighs of the patients. Similarly, previous Indian studies too have found that the occurrence rate of eschar varied from 1.8 to 24%.38 Takhar et al, Sivarajan et al, and Subbalaxmi et al reported presence of eschar in 13.7%, 1.8%, 12.1%, 11.1%, and 13.1% of the cases. [22-25] This may be attributed to the dark color of skin in Indians.

In our study, atypical presentation cases were observed like hepatitis, bleeding disorder, ptosis, altered sensorium. Majority of them had symptoms of tiredness and anorexia. Patients were presented through increased levels of SGOT and SGPT. The most common atypical presentation was hepatitis among 37.1% of patients. On examination, hepatomegaly was found in 21.5% patients whereas

splenomegaly in 18.4% patients. Previous studies showed that 7.40% had acute hepatitis, hepatomegaly in eight cases, 14.8%, while splenomegaly in one case, 1.85%. [20,26] Results were similar to that obtained from a study conducted by Narvencar KP et al showing that hepatomegaly was in 6.9% of cases whereas splenomegaly in 13.7% cases. [27] In study done by Zhang M et al, abnormal liver function test was the most common laboratory result.[21]

Acute kidney injury occurred in 25.7% cases in those patients who had history of decreased urine output. All of these patients recovered without hemodialysis with the help of conservative fluid management. 12% to 22% patients were seen to have acute kidney injury in the studies by Pathania M et al, Subbalaxmi MVS et al and Griffith M et al.[20, 23, 28] Acute encephalitis syndrome (AES) features were found in 22.9% patients. Out of these 22.9% cases of AES, 22% patients showed signs of meningeal irritation like neck rigidity and/ or Kernig's sign. So, the sensitivity of these signs in Scrub typhus induced meningoencephalitis was high which was consistent with the previous studies done on patients of bacterial meningitis in which neck rigidity was 46.1% sensitive and Kernig's sign was 22.9% sensitive.

In a study by Sonthayanon and colleagues, a significant positive correlation was observed between higher bacterial DNA load at presentation and both mortality and duration of hospital stay (p=0.000). Although this finding suggests that bacterial load may serve as a useful prognostic marker, its practical application in resource-limited settings remains challenging because of the high costs associated with molecular testing.[29] In another retrospective epidemiological study, Lee et al. identified the absence of an eschar, higher APACHE II scores, and intensive care unit (ICU) admission as independent predictors of mortality among patients with scrub typhus (n=297; deaths=18).[30] These findings differed from those reported by Sonthayanon et al., who had previously demonstrated a significant association between the presence of an eschar, higher DNA load at presentation, and increased mortality. Owing to these conflicting observations, along with limited evidence and relatively small sample sizes, definitive conclusions regarding prognostic indicators in scrub typhus remain elusive. Further large-scale studies are warranted to clarify these associations. Despite appropriate management, five patients in the present study succumbed to the disease. All of them had developed multiorgan dysfunction. Among these patients, two experienced severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, one developed acute renal failure, and two had extensive pneumonia. Mortality was primarily attributable to severe complications, including ARDS, renal failure, and hepatic dysfunction.

The current study was one of those rare studies in West Bengal which assessed spectrum of clinical profile among scrub typhus meningoencephalitis patients. This study has some limitations. First, it was a single-center study conducted at a tertiary care hospital in one district of West Bengal. Second, the relatively small sample size restricted the assessment of long-term outcomes and temporal relationships between clinical, laboratory, and radiological parameters. A larger multicentric longitudinal study would provide more robust evidence regarding disease progression and treatment outcomes.

CONCLUSION

Scrub typhus meningoencephalitis should be considered as an important differential diagnosis in young patients from rural backgrounds who present with fever of 7–10 days' duration accompanied by altered sensorium and neck rigidity. Clinical features that may raise suspicion of scrub typhus include the presence of an eschar, signs of pneumonitis, manifestations of acute encephalitis syndrome, oliguria, and jaundice. Laboratory findings that support the diagnosis include anemia, leukocytosis, thrombocytopenia, elevated liver transaminases (SGOT/SGPT), increased blood urea and serum creatinine levels, and hypoalbuminemia. Prompt recognition of the disease and initiation of appropriate antimicrobial therapy are crucial for improving outcomes and reducing the risk of serious complications in patients with scrub typhus meningoencephalitis.

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