

# The clinical biochemical and hematological profile of scrub typhus meningoencephalitis



Souvik Sarkar<sup>1</sup>, Soumya Sarathi Mondal<sup>2</sup>, Enamul Hossain<sup>3</sup>, Souvik Kumar Das<sup>4</sup>,  
Rahul Kumar<sup>5</sup>, Sanjay Kumar Mandal<sup>6</sup>

<sup>1,3,4,5</sup>Junior Resident, <sup>2,6</sup>Professor, Department of General Medicine, Medical College and Hospital, Kolkata, West Bengal, India

Submission: 06-07-2023

Revision: 30-09-2023

Publication: 01-12-2023

## 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

### Access this article online

**Website:**

<http://nepjol.info/index.php/AJMS>

**DOI:** 10.3126/ajms.v14i12.52690

**E-ISSN:** 2091-0576

**P-ISSN:** 2467-9100

Copyright (c) 2023 Asian Journal of Medical Sciences



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

## 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.<sup>1</sup> With a case fatality rate of 30% (if left untreated), it is one of the most important re-emerging infections in India.<sup>2</sup> 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.<sup>3</sup>

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

### Address for Correspondence:

Dr. Sanjay Kumar Mandal, Professor, Department of General Medicine, Medical College and Hospital, Kolkata, West Bengal, India.

**Mobile:** +91-9830114591. **E-mail:** sanjaypgcal@yahoo.co.in

far is meningoencephalitis.<sup>4</sup> 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



**Figure 1:** Demonstrating right lateral rectus palsy



**Figure 2:** Maculopapular rash noted on left forearm



**Figure 3:** Eschar noted on the left leg

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.<sup>5</sup> 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.<sup>6</sup> 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  $5 \pm 1.044$  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.<sup>4,7,8</sup> Cranial nerve involvement, particularly unilateral or bilateral sixth nerve palsies, is sparsely reported.<sup>9</sup> 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.<sup>10</sup>

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  $10.3 \pm 2.33$  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.<sup>11</sup> 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.<sup>12</sup>

The most common electrolyte abnormality in our study was hyponatremia (83.3%). The mean sodium value in the study was found to be  $129.83 \pm 6.41$  mEq/L (Table 3). It has been reported in varying frequencies from several studies, both in adult and pediatric populations.<sup>13-15</sup> 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  $3.74 \pm 0.68$  mEq/L. In a study encompassing 502 patients of scrub typhus, Sedhain and Bhattarai had reported that only 1.34% of them had hypokalaemia.<sup>14</sup>

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 =  $507.16 \pm 1000.53$  units/L, SGPT =  $273.41 \pm 613.68$  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.<sup>16</sup>



**Table 1: The clinical features of the case subjects**

Case no. (CN)	Age	Sex	Religion	Presentation	Fever duration (days)
CN1	25	Female	Muslim	Fever, headache, vomiting, altered sensorium	5
CN2	20	Female	Hindu	Fever, headache, Jaundice, diplopia, altered sensorium, seizures	6
CN3	53	Female	Hindu	Fever, Headache, Neck Pain, altered sensorium	3
CN4	17	Male	Muslim	Fever, headache, altered sensorium, eschar	5
CN5	55	Female	Muslim	Fever, headache, altered sensorium	4
CN6	15	Male	Muslim	Fever, headache, altered sensorium	5
CN7	21	Female	Hindu	Fever, headache, altered sensorium	5
CN8	14	Male	Hindu	Fever, altered sensorium, headache, vomiting, maculopapular rash, seizures	6
CN9	48	Male	Hindu	Fever, headache, convulsions	7
CN10	23	Male	Hindu	Fever, headache, convulsions, altered sensorium	5
CN11	70	Male	Hindu	Fever, headache, neck pain	4
CN12	50	Male	Hindu	Fever, headache, altered sensorium, convulsions, eschar	5

**Table 2: The hematological features of the case subjects**

Case no. (CN)	Hemoglobin (g/dl)	Total leukocyte count (/mm <sup>3</sup> )	Platelet count (/mm <sup>3</sup> )
CN1	11.5	9120	199000
CN2	8.8	8490	216000
CN3	6.1	2150	32000
CN4	14.4	12830	227000
CN5	9.4	12530	167000
CN6	7.6	620	37,000
CN7	9.9	6200	408000
CN8	10.1	5440	179000
CN9	13.7	10680	218000
CN10	11.6	7000	436000
CN11	10	6500	150000
CN12	10.8	12100	140000

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<sup>3</sup>) 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  $66.67/\text{mm}^3 \pm 100.48$  cells/mm<sup>3</sup>, mean CSF protein was  $65.75 \pm 35.60$  mg/dL, and mean CSF glucose was  $73.58 \pm 19.90$  mg/dL (Table 4). These findings are concordant with other studies.<sup>15,17</sup>

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.<sup>18</sup>

Venkatesan and Eswaradass concluded in their study that meningoencephalitis with altered LFT should raise the suspicion of scrub typhus meningoencephalitis.<sup>19</sup>

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 3: The biochemical features of the case subjects**

Case No.	Serum Na (mEq/L)	Serum Potassium (mEq/L)	Serum Urea (mg/dl)	Serum Creatinine (mg/dl)	C-Reactive Protein (mg/dl)	SGOT (IU/ml)	SGPT (IU/ml)	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	Serum Globulin (g/dl)	Albumin (g/dl)	Prothrombin Time (seconds)
CN1	140	3.1	13	0.7	100.9	24	52	0.4	0.2	2.8	3.1	16.9
CN2	126	4.5	33	0.6	9.8	181	133	4.8	2.7	4.2	2.2	23.2
CN3	129	2.9	41	1.2	104.3	45	50	1	0.4	3	3.3	14.1
CN4	135	3.8	28	1.1	23	46	43	0.7	0.3	3.4	3.5	15.2
CN5	132	3.8	14	0.7	22.7	208	145	0.7	0.3	2.7	2.4	19.7
CN6	121	3.7	22	0.9	7.8	3271	156	0.5	0.2	2	2.9	20.5
CN7	136	3.6	12	0.7	8.3	16	12	0.4	0.2	4.4	3	16.6
CN8	134	3.3	29	0.8	21.7	1804	2215	3.6	2	3.9	3.4	18.6
CN9	130	4.8	25	0.8	79.9	82	80	0.9	0.3	4	4	16.2
CN10	125	2.9	24	0.9	107	152	83	0.4	0.2	3.1	2.5	16.4
CN11	132	4.9	170	4.3	66.2	147	182	1.6	0.8	3.7	1.6	12.6
CN12	118	3.6	63	1.4	95.7	110	130	1.3	0.6	6.5	2.5	13

**Table 4: CSF features of the 12 case subjects**

Case no. (CN)	CSF cell count (/mm <sup>3</sup> )	CSF cell type		CSF glucose (in mg/dl)	CSF protein (mg/dl)
		Neutrophils (%)	Monocytes (%)		
CN1	201	63	37	113	38
CN2	75	80	20	66	162
CN3	7	0	100	65	43
CN4	20	10	90	64	67
CN5	60	10	90	58	103
CN6	8	0	100	67	72
CN7	6	0	100	53	56
CN8	10	10	90	93	30
CN9	335	30	70	68	61
CN10	50	40	60	62	54
CN11	30	30	70	65	48
CN12	10	0	100	109	55

CSF: Cerebrospinal fluid

## REFERENCES

- Chakraborty S and Sarma N. Scrub typhus: An emerging threat. *Indian J Dermatol.* 2017;62(5):478-485. [https://doi.org/10.4103/ijd.IJD\\_388\\_17](https://doi.org/10.4103/ijd.IJD_388_17)
- Griffith M, Peter JV, Karthik G, Ramakrishna K, Prakash JA, Kalki RC, et al. Profile of organ dysfunction and predictors of mortality in severe scrub typhus infection requiring intensive care admission. *Indian J Crit Care Med.* 2014;18(8):497-502. <https://doi.org/10.4103/0972-5229.138145>
- Kundavaram AP, Jonathan AJ, Nathaniel SD and Varghese GM. Eschar in scrub typhus: A valuable clue to the diagnosis. *J Postgrad Med.* 2013;59(3):177-178. <https://doi.org/10.4103/0022-3859.118033>
- Misra UK, Kalita J and Mani VE. Neurological manifestations of scrub typhus. *J Neurol Neurosurg Psychiatry.* 2014;86(7):761-766. <https://doi.org/10.1136/jnnp-2014-308722>
- Mallick SK, Hazra S, Nandi T and Sarkar A. Scrub typhus: A hospital-based study in the Northern districts of West Bengal, India. *Int J Res Med Sci.* 2019;7(6):2403-2407. <https://doi.org/10.18203/2320-6012.ijrms20192537>
- Ravi V, Hameed SK, Desai A, Mani RS, Reddy V, Velayudhan A, et al. An algorithmic approach to identifying the aetiology of acute encephalitis syndrome in India: Results of a 4-year enhanced surveillance study. *Lancet Glob Health.* 2022;10(5):e685-e693. [https://doi.org/10.1016/S2214-109X\(22\)00079-1](https://doi.org/10.1016/S2214-109X(22)00079-1)
- Varghese GM, Mathew A, Kumar S, Abraham OC, Trowbridge P and Mathai E. Differential diagnosis of scrub typhus meningitis from bacterial meningitis using clinical and laboratory features. *Neurol India.* 2013;61(1):17-20. <https://doi.org/10.4103/0028-3886.107919>
- Kar A, Dhanaraj M, Dedeepiya D and Harikrishna K. Acute encephalitis syndrome following scrub typhus infection. *Indian J Crit Care Med.* 2014;18(7):453-455. <https://doi.org/10.4103/0972-5229.136074>
- Lee YH, Yun YJ and Jeong SH. Isolated abducens nerve palsy in a patient with scrub typhus. *J AAPOS.* 2010;14(5):460-461. <https://doi.org/10.1016/j.jaapos.2010.06.016>
- Shikino K, Ohira Y and Ikusaka M. Scrub typhus (tsutsugamushi disease) presenting as fever with an eschar. *J Gen Intern Med.* 2016;31(5):582. <https://doi.org/10.1007/s11606-015-3371-x>

11. Sharma N, Biswal M, Kumar A, Zaman K, Jain S and Bhalla A. Scrub typhus in a tertiary care hospital in North India. *Am J Trop Med Hyg.* 2016;95(2):447-451.  
<https://doi.org/10.4269/ajtmh.16-0086>
12. Naoi T, Morita M, Kawakami T and Fujimoto S. Hemophagocytic lymphohistiocytosis associated with scrub typhus: Systematic review and comparison between pediatric and adult cases. *Trop Med Infect Dis.* 2018;3(1):19.  
<https://doi.org/10.3390/tropicalmed3010019>
13. Verma SK, Gupta KK, Arya RK, Kumar V, Reddy DH, Chaudhary SC, et al. Clinical and biochemical profile of scrub typhus patients at a tertiary care hospital in Northern India. *J Family Med Prim Care.* 2021;10(3):1459-1465.  
[https://doi.org/10.4103/jfmpc.jfmpc\\_1162\\_20](https://doi.org/10.4103/jfmpc.jfmpc_1162_20)
14. Sedhain A and Bhattarai GR. Renal manifestation in scrub typhus during a major outbreak in Central Nepal. *Indian J Nephrol.* 2017;27(6):440-445.  
[https://doi.org/10.4103/ijn.IJN\\_133\\_17](https://doi.org/10.4103/ijn.IJN_133_17)
15. Jain D, Nand N, Giri K and Bhutani J. Scrub typhus infection, not a benign disease: An experience from a tertiary care center in Northern India. *Med Pharm Rep.* 2019;92(1):36-42.  
<https://doi.org/10.15386/cjmed-1088>
16. Park MJ, Lee HS, Shim SG and Kim SH. Scrub typhus associated hepatic dysfunction and abdominal CT findings. *Pak J Med Sci.* 2015;31(2):295-299.  
<https://doi.org/10.12669/pjms.312.6386>
17. Jamil MD, Hussain M, Lyngdoh M, Sharma S, Barman B and Bhattacharya PK. Scrub typhus meningoencephalitis, a diagnostic challenge for clinicians: A hospital based study from North-East India. *J Neurosci Rural Pract.* 2015;6(4):488-493.  
<https://doi.org/10.4103/0976-3147.169769>
18. Alam A, Agarwal P, Prabha J, Jain A, Kalyan RK, Kumar C, et al. Prediction rule for scrub typhus meningoencephalitis in children: Emerging disease in North India. *J Child Neurol.* 2020;35(12):820-827.  
<https://doi.org/10.1177/0883073820933148>
19. Eswaradass PV, Eswaradass C. Clinical, laboratory findings and complications of scrub typhus meningoencephalitis: Case series (I7-5D). *Neurol.* 2015;84(14 Supplement):I7-5D.

**Authors Contribution:**

**SS-** Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **SKM-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SSM-** Coordination and manuscript revision; **EH-** Review manuscript and statistical analysis; **SKD-** Review manuscript; **RK-** Review manuscript.

**Work attributed to:**

Medical College and Hospital, Kolkata, West Bengal, India.

**Orcid ID:**

Souvik Sarkar - <https://orcid.org/0000-0002-0662-6333>  
Soumya Sarathi Mondal - <https://orcid.org/0000-0002-4838-7780>  
Enamul Hossain - <https://orcid.org/0000-0002-6283-1665>  
Souvik Kumar Das - <https://orcid.org/0000-0002-4689-0104>  
Rahul Kumar - <https://orcid.org/0000-0001-5831-3665>  
Sanjay Kumar Mandal - <https://orcid.org/0000-0002-2925-056X>

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