

Scrub Typhus in Paediatric Age Group at a Tertiary Care Centre of Eastern India: Clinical, Biochemical Profile and Complications

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ABSTRACT

Background: Scrub typhus is a reemerging zoonosis, which presents as acute febrile illness. Very few paediatric prospective studies on this disease are reported from Eastern India. This prospective observational study was carried out to study the clinical presentation, diagnosis, complications and immediate outcome of Scrub typhus in paediatric population in a tertiary care hospital from Eastern India. **Material and Methods:** Totally 209 cases between 1 month and 18 years of age were included. Clinical manifestations, laboratory parameters and immediate outcome of all patients were recorded. All the data were collected and plotted in Microsoft Excel master chart. Continuous data were presented as mean \pm standard deviation (SD) and categorical data as frequency and percentage. All the data analysis was performed using statistical software IBM Statistical Package for the Social Sciences (SPSS) version 20.0. **Results:** Highest number of cases (41.1%) were found between 1 year and 5 years age group. Fever was the presenting complaint in all cases. Other common symptoms were cough (34%), pain abdomen (23.4%), vomiting (23%), seizure (11.5%) and altered sensorium (9.6%). Hepatomegaly was found in 56.5% and splenomegaly in 39.7% cases. Eschar was found in 27.3% cases. C-reactive protein was elevated (>10 mg/L) in 93.3% children. Other complications were pneumonitis (20.6%), meningoenzephalitis (12.4%), septic shock (8.6%), acute respiratory distress syndrome (5.7%), myocarditis (4.8%) and acute kidney injury (4.3%). Mortality was low (1%). **Conclusion:** Scrub typhus is not uncommon in paediatric population and it must be considered as a close differential diagnosis of any acute febrile illness even when classical clinical presentations are not found. Early treatment results in favourable outcome.

Keywords: AKI, chigger, eschar, IgM ELISA, pneumonitis

Introduction

Scrub typhus is the most commonly reported rickettsial infection in India with causative organism being *Orientia tsutsugamushi*.^[1,2] Scrub typhus is usually underdiagnosed in our country due to varied presentation, limited knowledge about the disease, low

index of suspicion among physicians and nonavailability of diagnostic facilities in community.^[3] Clinical manifestations can vary from mild to severe. It can affect almost all organ systems and can be fatal. Due to the high risk of dangerous complications and prompt response to doxycycline, timely diagnosis and treatment are important. Most of the studies of rickettsial infections in India and worldwide are on adult populations.^[1,4] In Indian subcontinent, there are scarce studies available regarding incidence and clinical profile in paediatrics scrub typhus, out of which majority are retrospective studies or sporadic case reports.^[5-7] Hence, this study (a prospective observational study)

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has been undertaken to study clinical features and complications of paediatric scrub typhus in a tertiary care centre of Eastern India. This study may help in contributing our experiences with primary care physicians, as scrub typhus having nonspecific symptoms often leads to misdiagnosis. Present study may provide clues for primary care physicians to diagnose and manage scrub typhus cases early, so that the complications can be preventable.

Materials and Methods

This study was a prospective observational study done in a tertiary care hospital of Odisha over a period of 2 years (September 2018 to August 2020). Clearance from Institutional Ethics Committee was taken prior to starting the study. All Children admitted between age group of 1 month and 18 years with diagnosis of scrub typhus (by detecting scrub typhus IgM by ELISA method) were included in the study. Infants and those who left against medical advice were excluded from the study.

The Scrub Typhus Detect™ IgM ELISA was used for detection of IgM antibodies in human serum to *Orientia tsutsugamushi*-derived recombinant antigen. A cut-off value of >0.14 is taken to define case positivity which had a sensitivity of 77.3% and specificity of 71.4%.^[8] In all children relevant information including age, sex, presenting symptoms, signs and clinical examination findings were collected in a predesigned proforma. Laboratory tests like Complete Blood Count, C-reactive protein (CRP), Liver Function Test (LFT), serum urea, creatinine (Cr), serum electrolytes, prothrombin time (PT), blood culture/sensitivity, urine culture/sensitivity and chest X-ray were done. Other laboratory tests such as lumbar puncture and cerebrospinal fluid (CSF) study were done in some patients when clinically indicated.

Acute kidney injury (AKI) is defined by KDIGO 2012 criteria; rise in serum Cr by ≥ 0.3 mg/dl within 48 h; or rise in serum Cr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 h. For staging, 2012 AKI staging criteria was used.^[9] Hepatic dysfunction was defined as serum bilirubin > 1 mg/dL, serum aspartate aminotransferase (AST) > 80 U/L, serum alanine aminotransferase (ALT) > 80 U/L, serum albumin < 3 g/dL and PT ≥ 15 sec. All the data were collected and plotted in Microsoft Excel master chart. Continuous data were presented as mean \pm standard deviation (SD) and categorical data as frequency and percentage. All the data analysis was performed using statistical software IBM SPSS version 20.0.

Results

During the study period, total 218 cases were diagnosed as scrub typhus by IgM ELISA method. Total 209 patients were enrolled in the study after the exclusion criteria. The maximum number of cases were seen in the age group of 1 to 5 years with 86 cases (41.1%) and the age wise distribution is given in [Table 1]. Boys and girls constitute 62.7% and 37.3%, respectively, with male: female ratio of 1.68:1.

All 209 cases were presented with fever. Rest of the common symptoms were cough (34%), pain abdomen (23.4%), vomiting (23%), seizure (11.5%), altered sensorium (9.6%) and headache (5.7%). Hepatomegaly was found in 118 cases (56.5%) and splenomegaly in 83 cases (39.7%). Eschar was found in 57 cases (27.3%). Other findings found were edema (10.5%), lymphadenopathy (10%), oliguria (urine output < 0.5 ml/kg/h) (3.8%) and icterus (1.9%). Symptoms and signs are depicted in [Table 2]. On investigation, the mean TLC was 14.9 ± 10.4 ($\times 10^3/\mu\text{L}$) ranging from 4.1 to 45.6 ($\times 10^3/\mu\text{L}$). The mean haemoglobin value was 10.2 ± 1.4 g% (range 6.2 to 12.8 g%). The mean platelet count was 2.3 ± 1.1 ($\times 10^5/\mu\text{L}$) ranging from 0.25 to 6.75 ($\times 10^5/\mu\text{L}$). The mean serum sodium was 135.4 ± 3.8 mEq/L (range 125 to 145 mEq/L) and mean serum potassium was 4.0 ± 0.5 mEq/L (range 3.1 to 5.4 mEq/L). Leucocytosis was seen in 92 cases (44%), anaemia in 51 cases (24.4%), thrombocytopenia in 49 cases (23.4%), hyponatremia in 76 cases (36.4%) and hypokalemia in 24 cases (11.5%). The mean \pm SD value of CRP was 52.9 ± 35.7 mg/L (range 4 to 194 mg/L). CRP was elevated (> 10 mg/L) in 195 cases (93.3%). Very high CRP (> 50 mg/L) was found in 99 cases (47.4%) and extremely high CRP (> 100 mg/L) was found in 12 cases (5.7%).

The most common complication was pneumonitis, seen in 43 (20.6%) cases. Other complications seen in descending order of frequency were meningoencephalitis in 26 (12.4%) cases, septic shock in 18 (8.6%) cases, acute respiratory distress syndrome (ARDS) in 12 (5.7%) cases, myocarditis in 10 (4.8%) cases and AKI in 9 (4.3%) cases [Table 3].

In the LFT analysis, the mean TSB was 0.23 ± 0.6 mg/dL (range 0.1 to 4.8 mg/dL), mean ALT was 76.1 ± 48.2 U/L (range 11 to 363 U/L), mean AST was 122.9 ± 84.6 U/L (range 18 to 489 U/L), mean serum albumin was 3.3 ± 0.6 g/dL (range 2.1 to 4.5) and mean PT was 13.1 ± 2.3 s (range 11 to 21 s). Hepatic dysfunction was seen in 137 (65.6%) cases. Most common LFT abnormality was AST elevation (> 80 U/L) seen in 127 (60.5%) cases. ALT elevation (> 80 U/L) was seen in 57 (27.1%) cases. Hypoalbuminemia (< 3 g/dL) was seen in 21 (10%) cases. Hyperbilirubinemia (TSB > 1 mg/dL) was seen in 6 (2.9%) cases. Coagulopathy (PT ≥ 15 s) was seen in 5 (2.4%) cases.

The mean value of serum Cr was 0.3 ± 0.1 (range 0.1 to 1.1 mg/dL) and mean value of serum Cr after 48 h of baseline was 0.3 ± 0.2 (range 0.1 to 1.6 mg/dL). An increase in serum Cr to ≥ 1.5 times baseline was seen in a total of 8 cases. Urine volume < 0.5 ml/kg/h for a minimum of 6 h was also seen in 8 cases. As per the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline, 9 cases were diagnosed as AKI. As per KDIGO 2012 AKI staging criteria, out of 9 cases of AKI, 7 were found to have AKI stage 1 and the other two were found to have stage 2. None of the study subjects had AKI stage 3.

Scrub meningoencephalitis was diagnosed in 27 cases of scrub typhus by CSF study. CSF cell count was $25.2 \pm 13.2/\text{mm}^3$

Table 1: Age distribution

Age group	Frequency	Percentage
1 month-<1 year	37	17.7
1 years-<5 years	86	41.1
5 years-<10 years	52	24.9
10 years-18 years	34	16.3
Total	209	100.0

Table 2: Signs and symptoms

Signs and symptoms	Frequency	Percentage
Fever	209	100.0
Cough	71	34.0
Headache	12	5.7
Altered sensorium	20	9.6
Seizure	24	11.5
Pain abdomen	49	23.4
Vomiting	48	23.0
Icterus	4	1.9
Edema	22	10.5
Oliguria	8	3.8
Lymphadenopathy	21	10.0
Eschar	57	27.3
Hepatomegaly	118	56.5
Splenomegaly	83	39.7

Table 3: Complications of scrub typhus

Complications	Frequency	Percentage
Pneumonitis	43	20.6
Meningoencephalitis	26	12.4
Septic Shock	18	8.6
ARDS	12	5.7
Myocarditis	10	4.8
AKI	9	4.3

(range 8 to 56/mm³). All cases showed a lymphocytic predominance of CSF. The mean lymphocyte percentage was 89.8 ± 8.7% (range 70%–100%). CSF protein was moderately elevated (mean 84.2 ± 35.9 mg/dL, range 32 to 165 mg/dL) and glucose was almost normal (mean 62.9 ± 5.1 mg/dL, range 55 to 73 mg/dL).

The mean duration of hospital stay was 7.0 ± 2.1 days (range 1 to 16 days). Out of 209 cases, 33 (15.7%) cases required paediatric ICU care. Out of all 209 cases, 207 cases recovered and discharged while 2 died, one due to ARDS and other due to renal failure.

Discussion

Total number of cases included in our study was 209. Age group commonly affected was between 1 year and <5 years, which is similar to earlier study from India.^[10]

Our study showed male children outnumbering females with ratio of 1.68:1, similar observations were found by previous studies.^[8,10,11] Fever was the presenting complaint in all the cases, similar to earlier studies.^[8,10,11] Other presenting

symptoms were cough, pain abdomen, vomiting, seizure, altered sensorium and headache. Common examination findings were hepatomegaly (56.5%) and splenomegaly (39.7%) similar to another study.^[10] Eschar, the most pathognomonic sign of scrub typhus was found in 27.3% cases in our study, like some other studies.^[8,10] However, eschar was found only in 11.8% of cases in Pathak *et al.*^[11] So we can suggest that though eschar is characteristic of scrub typhus, it may not be found in most of cases and strong clinical suspicion is crucial in endemic areas after monsoon season. In this study, less common signs were edema, lymphadenopathy, oliguria and icterus.

On investigation, leukocytosis was seen in 44% and anaemia in 24.4%. Earlier studies also showed similar observations. Thrombocytopenia was present in 23.4% children, similar to the study from north-east.^[12] Hyponatremia was present in 36.4% cases in our study. Pathak *et al.*^[11] reported hyponatremia in 48.7% cases. We observed the mean value of CRP to be 52.9 ± 35.7 mg/L (range 4 to 194 mg/L). CRP was elevated (>10 mg/L) in most of the cases (93.3%), very high CRP (>50 mg/L) was found in 47.4% cases and extremely high CRP (>100 mg/L) was found in 5.7% cases. A similar result of elevated CRP (>6 mg/L) was reported by earlier studies.^[8,13]

We found hepatic dysfunction in 65.6% of cases. The most common LFT abnormality was AST elevation (>80 U/L) seen in 60.5% cases. ALT elevation (>80 U/L) was seen in 27.1% cases. Similar elevation of transaminases (ALT and AST) were also reported by earlier studies.^[10,12,14] We found hypoalbuminemia (<3 g/dL) in only 10% of cases. However, Sarangi *et al.*^[10] Dass *et al.*^[12] and Kumar *et al.*^[14] reported hypoalbuminemia in 38.4%, 52.2% and 54%, respectively. We found hyperbilirubinemia (TSB >1 mg/dl) as a less common feature (2.9%) cases, similar to earlier studies.^[10,12,14] In this study, coagulopathy (PT ≥15 s) was seen in 2.4% cases. Another study in Taiwan reported no coagulopathy.^[15]

The most common complication observed in our study was lung involvement (20.6%). Similarly, another study in Odisha and in Thailand have reported pneumonitis as the most common complication.^[10,13] In this study, second most common complication was meningoencephalitis (12.4%). Many studies have found similar incidence of meningoencephalitis.^[10,11,13] In our study, septic shock was seen in 8.6% of cases. This is comparatively less to study by Bhat *et al.*^[16] (25.8%). This difference may be due to early diagnosis and management. ARDS was found in 5.7% of cases similar to earlier studies.^[10,14] We observed myocarditis in 4.8% of cases, similar to previous studies.^[12,16] AKI was detected in 4.3% of cases, similar result was reported in a study from north east.^[12]

In our study, CSF analysis was done in 38 cases and 27 were diagnosed as scrub meningoencephalitis. CSF analysis showed lymphocytic predominance, moderate elevation of protein and normal glucose; similar to few Indian studies.^[17,18]

In this study, average hospital stay was 7 ± 2.1 days. Another study conducted in Odisha also reported average hospital stay 7.62 ± 4.46 days.^[8] The mortality rate in our study was 1% which is less than 15%, 12%, 9% and 4.7% reported by Kamarasu *et al.*,^[19] Palanivel *et al.*^[20] and Muthukrishnan *et al.*,^[21] respectively. This may be attributed to early referral to our centre, early diagnosis and treatment.

Scrub typhus is a neglected rickettsial disease prevalent in our country and is reemerging.^[22] For timely diagnosis, treatment and favourable outcome, high degree of suspicion and knowledge about geographical distribution and clinical manifestations is important. This study can provide clues for primary care physician to diagnose and treat scrub typhus early. In a resource-limited setting like ours, the primary care physicians can play a crucial role in preventing this grave clinical entity from transforming into a serious public health concern.

Key points

1. In absence of typical clinical presentation, scrub typhus must be considered one of the close differential diagnosis of acute febrile illness.
2. Hepatosplenomegaly, elevated AST and raised CRP are important clues for early diagnosis.
3. Pending serological confirmation for diagnosis of scrub typhus, clinical suspicion warrants immediate starting of empirical therapy with doxycycline or azithromycin, as delay in treatment would result in fatal complications.

Ethical approval

Approved by Institutional Ethics Committee, Kalinga Institute of Medical Sciences, Bhubaneswar (KIIT/KIMS/IEC/165/2018, Dated 19th Sept 2018).

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Conflicts of interest

There are no conflicts of interest.

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