

Clinical spectrum and laboratory profile of scrub typhus in children: A study from tertiary care hospital in Uttarakhand, Northern India



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ABSTRACT

Background: Scrub typhus is a mite-born disease scrub. It commonly manifests as an acute febrile illness with multi-system involvement. It is regarded as a life-threatening disease in children, with serious complications usually occurring in the 2nd week of illness.

Aims and Objectives: The aims of this study were to explore the clinical and laboratory profile of children with scrub typhus. **Materials and Methods:** All children admitted with scrub typhus over 1-year duration were enrolled in the study. The clinical, laboratory profile, and outcome were observed and analyzed. **Results:** A total of 47 children were diagnosed with scrub typhus, 17 (36.1%) children had clinical and laboratory evidence of meningitis. The most frequent presenting features were fever (100%), headache (82.4%), vomiting (82.4%), seizures (41.2%), and altered sensorium (70.6%). The mean duration of fever was 6.57 days, eight children (7%) had persistent fever for >14 days duration. Other complications reported were hepatitis 2 (4.3%), hepatosplenomegaly in 18 (38.3%) acute respiratory distress syndrome 2 (4.3%), and shock 31 (66%). The mean cerebrospinal fluid (CSF) protein, glucose, and cell count was 65.75 ± 9.27 mg/dL, 45.00 ± 7.23 mg/dL, and 65.94 ± 52.72 cells/mm³ of CSF, respectively, with lymphocyte count of more than 96% in all cases. Most patients had lymphocytic pleocytosis and the mean lymphocyte percentage was 96.2% ± 4.5%. Out of all 47 patients, 45 (84.61%) patients recovered with appropriate antibiotics in both groups, while two (15.38%) patients expired in the group without meningitis. **Conclusion:** A high degree of suspicion and knowledge of the geographical distribution of Rickettsial diseases is crucial for its early diagnosis and favorable outcome. Scrub typhus should be considered in the differential diagnosis of aseptic meningitis.

Key words: Scrub typhus; Eschar; Meningitis; Children

INTRODUCTION

Scrub typhus, also known as tsutsugamushi disease caused by *Orientia tsutsugamushi*, is the most common Rickettsial infection in India. The infection is transmitted through the larval mites or “chiggers” belonging to the family Trombiculidae. Small rodents, particularly wild rats of subgenus *Rattus*, are natural hosts for scrub typhus and humans are accidental hosts. The incidence of scrub typhus is higher among rural populations. Cases are more likely to have exposure to rodents at home or at

work, which expose them to the risk of encountering chiggers sitting in grass blades, bushes, and shrubs. The disease is seasonal in many parts of India, which correlates with the appearance and activity of mites.^{1,2} Scrub typhus commonly manifests as an acute febrile illness with multi-system involvement. The usual initial presentation is fever with headache, congested face, and lymphadenopathy. Serious complications usually occur in the 2nd week of illness, which include acute respiratory distress syndrome (ARDS), pneumonia, meningitis, acute kidney injury, myocarditis, severe thrombocytopenia, and

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bleeding.^{3,4} Other neurological complications include seizure, cranial nerve deficits, vasculitis cerebral infarct, brain hemorrhages, polyneuropathy, sensorineural hearing loss, and meningitis.⁵⁻⁸ These manifestations may be due to direct invasion of central nervous system (CNS) by the organism as has been shown by polymerase chain reaction of cerebrospinal fluid (CSF) or may be due to the unique propensity of the organism to infect vascular endothelial cells, thereby causing micro infarct.⁹ The purpose of this study was to characterize the clinical and laboratory findings in children with scrub typhus.

Aims and objectives

-To study the clinical and laboratory spectrum of scrub typhus in children.

-To compare the children admitted with scrub typhus with and without meningitis.

MATERIALS AND METHODS

A prospective observational study was conducted in the Department of Pediatrics at a tertiary care teaching hospital, Dehradun, Uttarakhand. The duration of the study was 12 months.

Inclusion criteria

All children up to 18 years of age with undifferentiated febrile illness lasting for 5 or more days with or without eschar were screened for scrub typhus and investigated accordingly. Serologically confirmed scrub typhus cases were enrolled in the study. The diagnosis was confirmed by IgM ELISA test (Scrub typhus detect TM IgM ELISA system, in BiOS International, Inc. Seattle, USA). Scrub typhus meningitis was diagnosed by CSF analysis, those having a CSF pleocytosis of 5 cells/mm³ with CSF stains (India ink, acid-fast bacilli, and Grams stains) and cultures. Common infectious conditions that could clinically mimic scrub typhus were ruled out by performing the following tests: peripheral blood smear and rapid antigen test for malaria, dengue (NS1 antigen, IgM antibody) test, IgM typhi dot for enteric fever, urine routine-microscopy, and blood cultures. Patients were treated with a 10-day course of antibiotics (doxycycline 4 mg/kg/day in two divided doses or azithromycin 10 mg/kg/day and chloramphenicol 100 mg/kg/day).

Data so collected were tabulated in an excel sheet, under the guidance of a statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as Chi-square test and the level of significance was set at P<0.05.

Ethical clearance was taken from the Institutional Ethical Committee.

RESULTS

A total of 47 children were diagnosed with scrub typhus during the study period. No obvious sex predilection was observed as there were 20 (42.6%) females in comparison to 27 (57.4%) males. The youngest patient in the cohort was 18 months and the oldest was 17 years. The mean age at presentation was found to be 8.8 years (SD±4.934) and a mean weight of 27.29 kg (SD±14.8). Eighty-two (71.3%) children belonged to the state of Uttarakhand, while 33 (28.7%) children were referred from other states, out of which the majority were from western Uttar Pradesh, as shown in Table 1.

All children diagnosed with scrub typhus presented with fever with a mean duration of 6.57 days. Headache was the second most predominant symptom found in 29 (61.7%) children. Significantly, eight children (7%) presented with fever of >14 days duration. Vomiting was present in 28 (60.2%) children and abdominal pain was present in 6 (12.8%). Eschar was found in 10 (21.4%) children. Scrub typhus meningitis was diagnosed in 17 (36%) cases. The altered sensorium in the form of a reduced level of consciousness, abnormal behavior, agitation, irritability, or irrelevant talk was documented in 12 (70.2%) of meningitis cases. Neck rigidity was noted in 10 (58.8%) cases, of which 5 (29.4%) patients had associated Kernig's sign. Generalized seizure was documented in 7 (41.2%) number of meningitis cases.

Other complications reported were hepatitis 2 (4.3%), hepatosplenomegaly in 18 (38.3%), ARDS 2(4.3%), and shock 31 (66%), as shown in Table 1. Among the major non-neurological complications, shock was present in 31 (66%) of total scrub patients, while, in non-meningitis patients, only 20 (66.7%) and in 11 patients (64.7%) among meningitis groups with significant difference (P<0.05).

However, on laboratory investigation, hemoglobin, cell counts, and platelet count have no significant difference between the meningitis and non-meningitis group, and all patients were found to have raised aspartate aminotransferase and alanine transaminase levels. CSF analysis was done in 17 patients of scrub typhus with clinical suspicion of meningitis. CSF analysis finding along with other neurological features and patients' outcome of all patients is shown in Table 2.

The mean CSF protein, glucose, and cell count were 65.75±9.27 mg/dL, 45.00±7.23 mg/dL, and 65.94±52.72 cells/mm³ of CSF, respectively, with

Table 1: Clinical profile of patients with scrub typhus

Variables	Overall (n=47)	Non-meningitis scrub typhus (n=30)	Scrub typhus meningitis (n=17)	P-value
Age (years)	8.88±4.85	9.53±4.77	7.72±4.93	NS
Weight (kg)	27.29±14.82	29.35±15.33	23.65±13.57	NS
Male/Female	27 (57.4%)/20 (42.6%)	17 (56.7%)/13 (43.3%)	10 (58.8%)/7 (41.2%)	NS
Fever	47 (100.0%)	30 (100.0%)	17 (100.0%)	NS
Fever duration (days±SD)	6.57±3.04	7.20±3.16	5.47±2.52	NS
Headache	29 (61.7%)	15 (50.0%)	14 (82.4%)	NS
Vomiting	28 (60.2%)	14 (46.6%)	14 (82.4%)	NS
Pain Abdomen	6 (12.7%)	5 (16.6%)	1 (5.9%)	NS
Eschar	10 (21.2%)	8 (26.6%)	2 (11.8%)	NS
Hepatitis	2 (4.3%)	2 (6.7%)	0	0.045#
ARDS	2 (4.3%)	2 (6.7%)	0	0.045#
Hepatomegaly	18 (38.3%)	14 (46.7%)	4 (23.5%)	0.001#
Splenomegaly	16 (34%)	12 (40.0%)	4 (23.5%)	0.001#
Shock	31 (66.0%)	20 (66.7%)	11 (64.7%)	0.002#

ARDS: Acute respiratory distress syndrome, #: Significant p-value (P<0.05)

Table 2: Laboratory parameters of scrub typhus patients

Parameters	Overall (n=47)	Non-meningitis scrub typhus (n=30)	Scrub typhus meningitis (n=17)	P-value
Hemoglobin (g/dL)	10.44±2.15	10.55±2.21	10.25±2.08	NS
Cell counts (mm ³)	11281.49±5169.50	10988.33±5638.14	11798.82±4332.23	NS
Neutrophils (%)	61.30±14.69	59.87±16.62	63.82±10.43	NS
Lymphocytes (%)	33.68±14.33	35.17±16.71	31.06±8.54	NS
Platelets (mm ³)	141448.51±98794.98	124700.00±58111.60	171004.71±143131.11	NS
AST (U/L)*	135.94±104.136	114.47±45.80	169.92±155.20	NS
ALT (U/L)**	106.06±81.72	87.58±55.43	135.33±108.00	NS

*AST: Aspartate aminotransferase, **ALT: Alanine transaminase

Table 3: CSF parameters in children with scrub typhus meningitis

CSF	Mean Value
TLC (cells/mm ³)	65.94±52.72
Polymorphs (%)	3.8±1.5
Lymphocytes (%)	96.2±4.5
Glucose (mg/dL)	45.00±7.23
Protein (g/dL)	65.75±9.27

CSF: Cerebrospinal fluid

lymphocyte count of more than 96% in all cases. Most patients had lymphocytic pleocytosis and the mean lymphocyte percentage was 96.2±4.5%, as shown in Table 3. Out of all 47 patients, 45 (84.61%) patients recovered, and 2 (15.38%) patients expired. Both two patients who expired had multiple organ dysfunctions.

DISCUSSION

In India, scrub typhus has been reported in at least 16 states.¹⁰⁻¹² Meningitis in childhood scrub typhus has not been extensively studied; most reports of meningitis are from Korea, India, and Taiwan. In most of the literature, meningitis was reported in 5–64% of children with scrub typhus.^{13,14} In our study, meningitis complicated 36% of

children with scrub typhus. A prospective study of Thai children revealed that scrub typhus was the second most common cause of aseptic meningitis next to Japanese encephalitis. Fever was documented in all cases of scrub typhus similar to observations by Digra et al., and Bhat et al. An eschar at the site of chigger bite can be seen in the early disease and is a useful diagnostic clue in scrub typhus, though its frequency varies from 7% to 97%.

Eschars are painless ulcers up to 1 cm in size, with a black necrotic center (resembling the mark of a cigarette burn). Usually, a single eschar is found on the neck, axillae, chest, abdomen, and groin, but multiple eschars have also been documented. In our study, only 10 (21.3%) children had eschar/rash at the time of admission. Hepatomegaly and splenomegaly were observed in 18 (38.3%) and 16 (34%), respectively, with significant difference among both the groups (P<0.01). The presence of splenomegaly is an important sign to distinguish scrub typhus from dengue fever as splenomegaly is uncommon in the latter.

Neck rigidity was noted in 10 (58.8%) patients of scrub typhus meningitis, similar to other studies showing the presence of neck rigidity in 45.45–49% of meningitis cases¹⁵ In our study, altered sensorium was noted in

12 (70.6%) and seizures were reported in 7 (41.2%) of meningitis patients. Other reports of seizure in patients with CNS involvement in scrub typhus vary from 22% to 50%.¹⁶

Most patients with scrub typhus meningitis had lymphocytic pleocytosis and mean lymphocyte percentage was $96.2 \pm 4.5\%$ with normal protein $65.75 \text{ mg/dL} \pm 9.27$ and $45.00 \text{ mg/dL} \pm 7.23$ glucose levels similar to one study¹⁷ contrast to other studies, where protein level was higher than normal.^{18,19}

Azithromycin is a preferred drug in children <8 years, while doxycycline is considered in older children. Doxycycline is bacteriostatic to *O. tsutsugamushi* and does not cross the blood–brain barrier (BBB) beyond 15–30%.²⁰⁻²² Chloramphenicol being a bactericidal drug with better BBB penetration is preferred in cases complicated with meningitis.²³ Rickettsial strains with reduced susceptibility to doxycycline have been reported, and alternative drugs can be used in such situations.²⁴⁻²⁵ The response to doxycycline is dramatic and fever persisting beyond 48 h of initiation of doxycycline should prompt consideration of alternative or additional diagnosis, including coinfection.²⁶

Limitations of the study

Relatively small sample size restricts the generalization of study, larger multi-centric studies are required for further implication of study.

CONCLUSION

Any child with acute febrile illness lasting for more than 5 days should be evaluated for scrub typhus for prompt treatment. In case of meningitis, scrub typhus should be kept in mind and empirical treatment should be started promptly for the early recovery. Early treatment with doxycycline or azithromycin should be considered in suspicious cases, as delay in treatment may lead to life-threatening complications.

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