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Prevalence, clinico-laboratory features and outcome of paediatric scrub typhus cases in a tertiary care centre in Eastern India

A prospective observational study

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Abstract

Objective: Scrub typhus is the most common rickettsial disease in India, caused by Orientia tsutsugamushi, and transmitted by chigger mites. Previously reported in South India, but the resurgence of cases is currently reported in Eastern India. This study aimed to estimate the prevalence and describe the clinico-laboratory profile of scrub typhus in paediatric patients (1-12 years old) in Eastern India. ***Methods:*** A prospective observational study was conducted from January to December 2019 in a paediatric tertiary care centre in Kolkata. All acute undifferentiated febrile illness cases (1-12 years) were tested for scrub typhus serology by ELISA. Demographic details, clinical features, laboratory findings, complications and treatment outcomes of scrub typhus patients were extracted in Microsoft Excel spreadsheet and further analysed. ***Results:*** The prevalence of scrub typhus among acute febrile illness patients was 4.5 %. The mean age of patients was 5.22 years and the majority (64.2 %) had a fever for the last 7-14 days. Gastrointestinal symptoms like vomiting (43.3 %) and pain abdominal (32.8 %) were frequently seen. Major clinical signs were hepatomegaly (41.8 %) and splenomegaly (31.3 %). Complication was observed in 74.6 %, with thrombocytopenia

(40.3 %) and meningoencephalitis (29.9 %) being more frequent. The case fatality rate was 1.5 %. ***Conclusions:*** Classical eschar was absent in three-fourth of our patients, hence we advocate laboratory scrub typhus testing for all suspected cases in endemic region. Thrombocytopenia and meningoencephalitis were prominent complications in our study. Prompt treatment with doxycycline and/or azithromycin could prevent complications and reduce mortality.

Keywords: Hospital Stay; Hospitalization, patient discharge; General Internal Medicine

Advances in Knowledge:

- To the best of author's knowledge, this is the first report of prevalence of scrub typhus among children with acute undifferentiated febrile illness in West Bengal, Eastern India.
- Compared to previous studies, a higher incidence of children developed scrub typhus related complications in our study. This may be due to delay in arrival up to the tertiary health care centre.

Application to Patient Care:

- Children with acute undifferentiated febrile illness for over 5 days, even without eschar should be tested for Scrub Typhus.
- Prominent gastrointestinal symptoms in children with acute undifferentiated febrile illness of over 5 days may be a symptom of scrub typhus.
- If facilities of testing are not available (e.g., in Community Health Centres), a child with acute undifferentiated febrile illness should be urgently referred to the higher centre without delay.

Introduction

Scrub typhus is caused by infection with a rickettsial bacteria *Orientia Tsutsugamushi* which is small Gram negative, obligate intracellular organism. *Orientia tsutsugamushi* is transmitted to humans by the bite of the larva of Trombiculite mite (chigger).[1] Infected chiggers are usually found in areas of heavy scrub vegetation during the wet season.[2] The disease is endemic in 'tsutsugamushi triangle' a geographic area, confined between South and Southeast Asia, Northern Australia, and the islands of the Indian and Pacific Oceans.[3] Globally one billion people are at risk and over one million infections occur each year due to

scrub typhus.[4] The risk factors of scrub typhus infection include agricultural work, residence location (in riverbanks, forest clearing, grassy region), poor sanitation around the house (which favours rodent infestation), vegetations in the house yard, close contact with domestic animals and poor occupational safety practices.[5]

World Health Organization identifies scrub typhus as an emerging disease in Southeast Asia with a case fatality rate of up to 30% if left untreated.[6] A resurgence of scrub typhus has been reported in India in recent times. The infection leads to acute febrile illness with symptoms overlapping with other viral and bacterial illnesses, and high morbidity and mortality.[7,8] Devasagayam et al.[9] conducted a systematic review to estimate the burden of scrub typhus across India. They reported that the resurgence of the disease is prominent in the South Indian, sub-Himalayan and North Indian states. There is limited data on the prevalence and trends of scrub typhus occurring in paediatric population in India. The majority of the scrub typhus studies in paediatric population are retrospective studies or isolated case reports.[10] In most parts of India there is a surge in the scrub typhus cases from July to November, which corresponds to monsoon and post-monsoon.[11,12] In south India some outbreaks have been reported in cooler months from September to January.[13]

Scrub typhus diagnostic methods are broadly classified into direct and indirect methods. Direct methods include isolation and culture of the bacteria, and diagnosis of the genetic material by polymerase chain reaction. Cell culture facility can be used for *in vitro* cultivation of the bacteria, but this is a time-consuming process, requires specialized laboratory with trained manpower, it has limited clinical utility. Molecular methods such as polymerase chain reaction have been developed to detect various genes (56kDa, 47kDa and *groEL* genes) of rickettsia. However, this is expensive and requires significant manpower training.[14,15] Indirect diagnostic methods aim to detect the *Orientia tsutsugamushi*-specific antibodies which appear in the affected individual due to humoral immunity. These methods include immunofluorescence assay (IFA), immunochromatographic test (ICT), enzyme-linked immunosorbent assay (ELISA), Weil–Felix test, and immunoperoxidase assays.[14] Immunofluorescence antibody (IFA) assay is considered as the gold standard for diagnosing rickettsial infections. In this test a mixture of antigens (Kato, Karp, Gilliam and any local serotypes) from the common strains of *Orientia tsutsugamushi* are usually used to detect antibodies in the patient serum. This antigen-antibody complex is thereafter detected using a fluorescently labeled anti-human antibody.[16,17] In the United States indirect

immunofluorescence antibody test for scrub typhus diagnosis is available in most public laboratories. This test is expensive and requires human resource training. However, fluorescence microscope instrument required to carry out this test is available at limited centres in developing countries like India. Weil-Felix test, which was the most widely used serological test for rickettsial screening has low sensitivity and specificity.[19] ELISA kits can rapidly detect scrub typhus antigen-specific IgM or IgG antibodies. These kits use *Orientia tsutsugamushi* recombinant p56kD type-specific antigen of Karp, Kato, Gilliam and TA716 strains, and have over 90% sensitivity and specificity for detecting scrub typhus-specific antibodies in blood.[20] Point of care testing (POCT) has also been recently developed for detection of scrub typhus.[15]

Acute febrile illness is a very common presentation in children living in tropical countries. Diagnosis is often challenging as different paediatric infectious diseases have common symptoms.[21] The infection clinically manifests as non-specific febrile illness, accompanied by myalgia, headache, and occasional rash, often associated with gastrointestinal, respiratory or central nervous system symptoms. Untreated cases may progress to severe multi-organ dysfunction. Identifying a paediatric scrub typhus case is challenging owing to varied presenting features, scarce knowledge about the disease and low index of suspicion among paediatricians.[10] But the availability of scrub typhus-specific ELISA kits at the Government run medical colleges and district hospitals are now helping paediatricians to rapidly detect scrub typhus in children with acute febrile illness. Early identification and treatment with doxycycline and/or azithromycin is reported to prevent complications and improve patient outcomes.[22] This study aims to estimate the prevalence and describe the clinico-laboratory profile of scrub typhus in paediatric patients (1-12 years old) in Eastern India.

Methods

This prospective observational study was conducted at Dr.B.C.Roy Post Graduate Institute of Paediatric Sciences, Kolkata a tertiary care centre in Eastern India, over one year (January 2019 to December 2019). Ethical clearance was taken from the Institutional Review Committee before starting the study. An information leaflet was provided and thereafter informed and written consent was taken from the parents of all children enrolled in this study.

Acute undifferentiated febrile illness of five days or more with or without eschar was suspected as a case of rickettsial infection (if eschar was present, fever of less than five days duration was considered as scrub typhus). A suspected clinical case with an optical density (OD) above 0.5 for scrub typhus IgM by ELISA was considered to be a probable case of scrub typhus.

Children (1-12 years of age) with acute undifferentiated febrile illness of over 5 days duration, who were admitted in the paediatric ward, whose scrub typhus IgM ELISA test was positive and who ordinarily resided in the Indian state of West Bengal, were included in this study. Children with acute undifferentiated febrile illness clinically suggestive of scrub typhus but reporting seronegative, those reporting positive for blood and/or urine culture, those reporting seropositive for dengue and those with congenital heart disease, nephrotic syndrome, chronic liver disease, severe acute malnutrition were excluded from the study. The febrile children having incomplete or missing data were excluded.

A convenient sampling method was used[23]. We calculated the sample size (n) based on the formula $n= (z\text{-score})^2 \times p \times q / e^2$. Taking a z-score of 1.645 at 90% confidence interval, prevalence (p) of scrub typhus in febrile children reported from a previous study as 3.15 %,[16] margin of error (e) of 1%, we calculated the sample size to be 826. After considering a non-response rate of 10%, the sample size came to be 909. But we included 1473 acute febrile children (1-12 years of age) who were admitted in our institute during our study period.

Scrub typhus IgM antibodies in patient serum was detected by indirect ELISA using Microlisa™ kits. As per the kit literature, the in-house evaluation of the kit has demonstrated a has a sensitivity of 100 % and specificity of 98.58%, while the external evaluation has depicted a sensitivity of 100 % and specificity of 100 %. If the scrub typhus IgM units was over 11, we interpreted the sample as positive for scrub typhus IgM antibodies. Those who tested positive for scrub typhus serology by ELISA test were included for further analysis based on the inclusion and exclusion criteria.

Based on the objectives of the study a proforma was pre-designed to record the history, examination findings and investigation reports of patients. Patients were enrolled in the study based on the inclusion and exclusion criteria. The pre-designed proforma was used to collect and record the detailed history including name, age, sex, date of admission, brief history,

clinical findings, investigation reports and outcome. The investigations included: complete blood count, liver function test, renal function test, prothrombin time, activated partial thromboplastin time, urine routine and microscopic examination, chest x-ray, ECG, echocardiography, ultrasonography of whole abdomen, cerebrospinal fluid examination (if required) and CT/USG brain (if required). An excel spreadsheet was used to record the main findings of the patient from the pre-designed proforma.

Standard criteria were used to define the various complications of scrub typhus. Anemia was considered when the hemoglobin level was less than 11 g/dl, less than 11.5 g/dl and less than 12 g/dl in the age groups 13-59 months, 5-11 years and 12 years respectively. A WBC count of 4000 – 11000/µl, platelet count of 150000 – 450000/µl, erythrocyte sedimentation rate of 0-10 mm/hour (in 1-12 y age group) and C-reactive protein of less than 3 mg/L was considered to be normal. When the rise in serum transaminases (AST/ALT) was more than twice the upper normal limit, liver enzymes was considered to be elevated. A urine output less than 500 mL/1.73 m^2 per day was considered as oliguria. Serum sodium level less than 135 mEq/L was considered as hyponatremia. A Glasgow Coma Scale of 7/15 to 10/15 was considered as altered sensorium. Altered sensorium along with signs of meningeal irritation and/or seizures associated with elevated protein and lymphocytic/neutrophilic cytology with normal/low CSF sugar was considered as meningoencephalitis. Dysfunction of more than one organ, requiring intervention to maintain homeostasis was considered multiple organ dysfunction syndrome.

Strict confidentiality was maintained throughout the study regarding the patient data utilized for the current study. The continuous data was checked for normality using the Kolmogorov-Smirnov test. The parametric data was presented as mean ± standard deviations, while the non-parametric data was presented as median and interquartile range. All the categorical data were presented as frequency and percentage. Data was analysed using IBM SPSS version 25.

Results

In our study, 1473 children (1-12 years age) were found to have been admitted with acute febrile illness. Among them, 67 were confirmed to be IgM-positive for scrub typhus. The prevalence of scrub typhus among children admitted with acute febrile illness was 4.5 % [(67/1473) x 100 % = 4.5 %]. On analysing sex-wise we observed that the prevalence of scrub typhus was 4.7% in female patients and 4.4% in male patients. However, when we

analysed the seropositive cases, we observed that the disease was more frequent among males (59.7 %) as compared to females (40.3 %). The mean age of these patients in our study was 5.22±3.05 years, with 38 (56.7 %) patients in the 1-5 years age group. The age and sex-wise prevalence of scrub typhus among children with acute febrile illness is presented in Table 1.

Fever was present in all 67 (100%) children in our study. The duration of fever was 6-7 days in 9 (13.4 %) children, 7-14 days in 43 (64.2 %) children and over 14 days for 15 (22.4 %) patients. The mean duration of fever in scrub typhus-positive patients was 10.67 ±3.90 days. Other symptoms in decreasing order of frequency were vomiting (n=29, 43.3 %), pain abdomen (n=22, 32.8 %), dyspnea (n=15, 22.4 %), cough (n=13, 19.4 %), diarrhoea (n=13, 19.4 %), convulsion (n=13, 19.4 %), altered sensorium (n=7, 10.4 %), oliguria (n=5, 7.5 %) and headache (n=5, 7.5 %). (Table 2)
On examination, hepatomegaly was seen in 28 (41.8 %) followed by splenomegaly in 21 (31.3 %), oedema in 16 (24.0 %), eschar in 16 (24.0 %), maculopapular rash in 14 (20.9 %), lymphadenopathy in 11 (16.4 %), meningeal signs in 8 (11.9 %), hypotension in 8 (11.9 %) and icterus in 4 (5.9 %) of patients. (Table 2)

Anemia was seen in 44 (65.7 %), leukocytosis in 35 (52.2 %), thrombocytopenia in 27 (40.2 %), raised erythrocyte sedimentation rate in 47 (69.1 %), raised C-reactive protein in 20 (29.9 %), elevated liver enzymes in 21 (31.3 %) and hyponatremia in 20 (29.9 %). Abnormal chest radiography was observed in 16 (23.9 %) patients. Whole abdomen ultrasonography gave the impression of hepatomegaly in 35 (52.5 %), hepatosplenosplenomegaly in 27 (43.3 %) and ascites in 21 (31.3 %) patients. (Table 3)

Out of 67 patients in our study, 50 (74.6 %) had developed complications. The most frequent complication observed in our study was thrombocytopenia in 27 (40.3 %) and meningoencephalitis in 20 (29.9 %) patients. Other complications noted are presented in Table 4. During treatment in our institute one patient had died.

Discussion

In this study, we carried out a prospective observational study on 1473 children hospitalized with acute febrile illness over one year to estimate the prevalence and describe the clinic-epidemiological profile of scrub typhus-positive patients. As the World Health Organization has declared scrub typhus as a re-emerging infectious disease in Southeast Asia with a case

fatality rate of 30 %,[6] it is important to identify and initiate treatment in the early stage. Out of 67 scrub typhus in our study majority (56.7 %) were in the 1–5 years age group, while the remaining (43.3 %) were over five years and up to 12 years age group (Table 1). Similar findings were reported by Gurunathan S R et al.[6] and Ganesh R et al. [24]. This might be because children in this age group play in outdoor for prolonged periods and are more likely to get exposed during that time. In our study the sex ratio (male:female) of scrub typhus patients is 1.48 : 1. Bhat N K et al.[25] and Basu S et al.[26] also reported that the disease was more frequent in male children. Due to social customs in most parts of India, boys are allowed to play outdoor games, while girls stay indoors.[27] During outdoor play the male children are more likely to be infected by the chiggers. Higher frequency of scrub typhus infection in male children was also reported from studies conducted in Thailand and Taiwan.[28,29]

We observed that the majority (64.2 %) of scrub typhus patients had a fever for the last 7-14 days with the mean duration of fever as 10.67 ± 3.90 days (Table 2). A similar duration of fever on hospital arrival was also reported by Bhat N K et al.[25], Basu S et al.[26] and Sah R K et al.[30]. This is likely as in the first week of acute febrile illness parents might have considered it to be of viral etiology and did not consult the paediatrician. But when the fever persisted for over a week and the patient was hospitalized, further investigation and treatment helped in the diagnosis of the disease.

In our study, vomiting (43.3 %) and pain abdomen (32.8 %) were the most common presentations associated with fever (Table 2). Aung-Thu SW et al.[31] reported that the predominance of gastrointestinal symptoms can help us to differentiate scrub typhus from other febrile illnesses like malaria, dengue and leptospirosis. The classical sign of eschar was noted in only 23.9 % of scrub typhus patients in our study. Kim DM[32] reported that eschar can be seen in 7% to 68% of cases of scrub typhus. Hence, the presence of eschar is a valuable clinical clue for diagnosis, however, its absence does not rule out the disease. We suggest that scrub typhus should always be considered as a differential diagnosis in patients presenting with acute undifferentiated febrile illness of over five days and gastrointestinal symptoms.

On performing a clinical examination, the most common findings in our scrub typhus patients were hepatomegaly (52.2 %) and splenomegaly (43.3 %) (Table 2). Hepatomegaly was

reported in 94.7 % by Ganesh et al.[24], 82 % by Bhat N K et al.[25] and 33.3 % of patients by Dass R et al.[33]. Splenomegaly was reported in 89.9 % by Ganesh et al.[24], 39 % by Bhat N K et al.[25] and 45.8 % by Dass R et al.[33]. In our study lymphadenopathy was observed in 16.4 % of patients, while it was reported in 17.7 % by Sah R K et al.[30], 38 % by Bhat N K et al.[25] and 59 % of patients by Basu S et al.[26]. These findings suggest that paediatric patients from endemic areas with acute febrile illness over 5 days should be thoroughly screened for hepatomegaly, splenomegaly and lymphadenopathy, which can help in starting treatment before serological reports arrive.

We observed that 50 out of 67 patients (74.6 %) had developed complications from scrub typhus infection. Thrombocytopenia (40.3 %) and meningoencephalitis (29.9 %) were the most frequent complications in our patients (Table 4). Meningoencephalitis was reported in 58.6 % by Lurshay RM et al.[34], 34.4 % by Basu S et al.[26], 30.3 % by Bhat N K et al.[25] and 6 % by Palanivel S et al.[35] A higher number of patients with complications was seen in our study. This may be because our institution is a tertiary centre where referral patients from district hospitals arrive for admission and further treatment. The case fatality rate in our study was 1.5%. The single patient who died was a 7-year-old male child who had presented with fever for 12 days with altered sensorium and generalized oedema. After treatment with doxycycline and/or azithromycin, a complete recovery with no post-meningoencephalitis sequel at the time of discharge was observed in other patients. Doxycycline is the drug of choice for treating scrub typhus. In children it may be given either orally or intravenously. For children weighing less than 40 kg, it is given at 2.2 mg/kg body weight twice daily. Those over 40 kg should be given 100 mg twice daily. The drug should be continued for three days after the fever subsides or for a total of seven days. Severe or complicated cases of scrub typhus may need antibiotic therapy till 10 days. If fever persists even after 48 hours of starting doxycycline therapy, alternative antibiotics should be initiated or further investigations should be done to rule out co-infection. Alternative antibiotics which may be given in scrub typhus include azithromycin, clarithromycin, chloramphenicol and rifampicin. In paediatric scrub typhus cases azithromycin is given at 10 mg/kg body weight/day for five days.[36,37]

Our study was not without limitations. We conducted this study in a referral tertiary level hospital. Therefore, the results may not reflect the actual burden of scrub typhus in the community. Our hospital is located in a metropolitan city in Eastern India. As chiggers are

present more in shrubs and bushes, this disease is likely to be more prevalent in the rural areas of districts. Due to the upgradation of rural district hospitals in recent years and the availability of ELISA-based scrub typhus kits there, many cases may now be detected and managed in the rural district hospitals. This may underestimate the disease burden in hospitals located in metropolitan cities. We used IgM ELISA kits to detect scrub typhus, rather than using indirect immunofluorescence assay, which is considered to be the gold standard.

Conclusion

Scrub typhus is an emerging cause of febrile illness in children from Eastern India. The classical eschar was not present in three-fourth of our patients, hence, we advocate laboratory test of scrub typhus for all acute febrile illness of over five days. Thrombocytopenia and meningoencephalities are prominent scrub typhus complications in our study. Prompt empirical therapy with doxycycline and/or azithromycin should be initiated, pending serological confirmation, to prevent life-threatening complications and mortality. In cases of outbreak, the state health and local rural or urban body should be notified so that they can clean the shrubs and bushes which will help to reduce disease transmission.

Author Contributions

All authors conceived, designed, and wrote the paper. RM carried out the data collection. AKB and GM supervised the work. All authors reviewed and interpreted the data. All authors approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interests.

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Table 1: Age and gender-wise prevalence of scrub typhus in children with acute febrile illness

			n (%)
Age group	1 to 5 years		38 (56.7 %)
	>5 to 12 years		29 (43.3 %)
	Total		67 (100%)
		Prevalence	**n (%)**
Sex	Male	40/904 (4.4 %)	40 (59.70 %)
	Female	27/569 (4.7 %)	27 (40.29 %)
	Total	67/1473 (4.5 %)	67 (100 %)

Table 2: Clinical characteristics of scrub typhus patients

Symptoms		**n (%)**
Fever	6-7 days	9 (13.4 %)
	7-14 days	43 (64.2 %)
	> 14 days	15 (22.4 %)
Vomiting		29 (43.3 %)
Pain abdomen		22 (32.8 %)
Dyspnea		15 (22.4 %)
Cough		13 (19.4 %)
Diarrhoea		13 (19.4 %)
Convulsion		13 (19.4 %)
Altered sensorium		7 (10.4 %)
Oliguria		5 (7.5 %)
Headache		5 (7.5 %)
Clinical findings		
Hepatomegaly		28 (41.8 %)
Splenomegaly		21 (31.3 %)
Oedema		16 (24.0 %)
Eschar		16 (24.0 %)
Maculopapular rash		14 (20.9 %)
Lymphadenopathy		11 (16.4 %)
Meningeal signs		8 (11.9 %)

Hypotension	8 (11.9 %)
Icterus	4 (5.9 %)

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456 **Table 3: Laboratory and radiological abnormalities of scrub typhus patients**

Parameter		**n (%)**
Anemia		44 (65.7 %)
Total leukocyte count	< 4000	3 (4.5 %)
	4000-11,000	29 (43.3 %)
	>11,000	35 (52.2 %)
Platelet count	< 50,000	3 (4.5 %)
	50000 – 1,00,000	17 (25.4 %)
	1,00,000- 1,50,000	7 (10.4 %)
	>1,50,000	40 (59.7 %)
Erythrocyte sedimentation rate > 10 mm /1st hour		47 (69.1 %)
Raised C-reactive protein		20 (29.9 %)
Elevated liver enzymes		21 (31.3 %)
Hyponatremia		20 (29.9 %)
Abnormal chest X-ray findings		16 (23.9 %)
Ultrasonography whole abdomen impression	Hepatomegaly	35 (52.2 %)
	Hepatosplenomegaly	27 (43.3 %)
	Ascites	21 (31.3 %)

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458 **Table 4: Complications in scrub typhus patients**

Complication	**n (%)**
Thrombocytopenia	27 (40.3 %)
Meningoencephalitis	20 (29.9 %)
Pneumonia	12 (17.9 %)
Shock	12 (17.9 %)
Pleural effusion	10 (14.9 %)
Hepatitis	6 (9.0 %)
Congestive cardiac failure	6 (9.0 %)
Acute respiratory distress syndrome	3 (4.5 %)
Acute kidney injury	2 (3.0 %)
Multiple organ dysfunction syndrome	2 (3%)
Pulmonary hemorrhage	1 (1.5 %)
Disseminated intravascular coagulation	1 (1.5 %)
Death	1 (1.5 %)

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