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Analysis of 262 Children with Scrub Typhus Infection: A Single-Center Experience

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Abstract. Scrub typhus, a vector-borne rickettsiosis, is the leading treatable cause of non-malarial febrile illness in Asia. The myriad of typical and atypical features poses a clinical conundrum. We aimed to study the clinical and laboratory profile of children with scrub typhus infection diagnosed by IgM ELISA. Data of children < 12 years presenting with undifferentiated fever to the pediatric services of a tertiary teaching institute between January 2012 and December 2018 were retrieved. Children with seropositive IgM ELISA (InBios International Kit, Seattle, WA) for scrub typhus were enrolled in the study. Clinical features, laboratory investigations, treatment received, and the outcome recorded were obtained. Objective evidence of organ dysfunction was taken as severe scrub typhus. In total, 262 children were diagnosed with scrub typhus. The mean age was 5 years, with male preponderance (65%). And, 13 children presented during infancy. Fever was universal, and generalized lymphadenopathy (93.5%) and hepatomegaly (70%) were the common clinical signs. Eschar was identified in 31%, with greater predilection for groin and axilla. Thrombocytopenia was striking in one-third of children. Also, 25 children (9.5%) had severe scrub typhus and 18 required intensive care stay. Elevated aspartate aminotransferase enzyme levels was a predictor of severity ([OR 3.9], *P* value 0.005) by multivariate analysis. Lymphadenopathy was found significantly associated with eschar ($P < 0.005$). No mortality was recorded. This 6-year study underscores the varied spectrum of pediatric scrub typhus infection. Zero mortality in our cohort signifies the excellent outcome with judicious first-line antibiotics.

INTRODUCTION

Scrub typhus, a vector-borne rickettsiosis caused by *Orientia tsutsugamushi* infection, is one of the leading causes of non-malarial febrile illness in Asia.[1] The disease presents as acute undifferentiated fever with or without eschar. The clinical picture is characterized by fever with chills, myalgia, headache, abdominal pain, vomiting, and capillary leak during the first week of illness. Its nonspecific clinical features and shared seasonal profile with dengue and leptospirosis hamper its early diagnosis, particularly in the tropics.[2] The pathophysiology is not entirely clear, though in general, it is assumed to be disseminated vasculitis with primary target being vascular endothelium. Complex interplay of host and pathogen response with combined humoral and cellular immunity contributes to the development of vascular injury to skin, lungs, liver, and brain.[3] The gold standard test for diagnosis, the indirect immunofluorescent assay, is prohibited by exorbitant cost and the need for personnel trained in fluorescent microscopy and is usually limited to research centers.[4] Laboratory confirmation, in resource-constrained settings, is commonly accomplished by IgM ELISA (InBios International Kit), with 91% sensitivity and 99% specificity.[5–7] The disease, in general, portends a mild phenotype with a median mortality of 6% (0–70%) if left untreated.[8] Complications of scrub typhus are organ-specific and comprise acute respiratory distress syndrome, acute kidney injury, myocarditis, meningoencephalitis, and disseminated intravascular coagulation.[9,10] Given the poorly defined symptomatology and life-threatening complications if left untreated, early diagnosis and judicious antibiotic therapy with tetracyclines/chloramphenicol is crucial. The research objective was to study the clinical profile of children with scrub typhus diagnosed by IgM ELISA admitted at a tertiary care teaching institute in South India with special reference to the myriad of typical and atypical manifestations.

METHODOLOGY

This study is a retrospective review of children with clinical and laboratory diagnosis of scrub typhus presenting to the Department of Paediatrics, Pondicherry Institute of Medical Sciences, a tertiary care teaching institute in South India, during the period of January 2012–December 2018. Children younger than 12 years presenting with acute undifferentiated fever, defined as acute febrile illness with onset in the previous 2 weeks with fever of > 38°C for at least 48-hour duration, were screened for eligibility. Children with seropositive IgM ELISA for scrub typhus were enrolled in the study. The InBios International Kit with a sensitivity of 91% and a specificity of 99% was used for diagnostic testing. A sample absorbance value > 0.5 was established as the cutoff criteria based on the local healthy normal sera. Children with classical symptoms and signs suggestive or diagnostic of a particular febrile illness (other than scrub typhus) or with chronic or recurrent febrile illness were excluded. Children with objective evidence of organ dysfunction such as myocarditis, meningoencephalitis, pneumonia, acute kidney injury, acute respiratory distress syndrome, disseminated intravascular coagulation, pancreatitis, and hemophagocytic lymphohistiocytosis were considered as severe scrub typhus. The study was approved by the Institutional Ethics Committee (IEC-RC/16/147). Waiver of parental consent was obtained from the Institutional Ethics committee because this was a retrospective chart review. Clinical features, laboratory investigations, treatment received, and the outcome recorded were obtained. The data were entered in a data recording form and then transcribed to MS Excel data and analyzed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL). Descriptive data were represented by frequency, percentage, and mean ± SD. The chi-square test for dichotomous variables and *t* test and

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Mann–Whitney *U* test for continuous variables were applied. The associations of clinical and laboratory variables were studied by multivariate regression and logistic regression. $P < 0.05$ was considered statistically significant.

RESULTS

During the period of January 2012–December 2018, records of 41,365 children presenting to the pediatric services with fever were reviewed, and a total of 262 children with undifferentiated fever and IgM ELISA positivity for scrub typhus were diagnosed. Of these, 170 were boys (65%) and more than half of the children were between the age-group of 1–5 years (Table 1). The youngest infant diagnosed was aged 5 months, and 13 children (5%) presented during infancy. Fever was universal, and 128 children presented within the first 5 days of fever (44%). Generalized lymphadenopathy (93.5%) and hepatomegaly (70%) were the most common clinical findings. Painless eschar was identified in 31% of children, with greater predilection for groin and axilla (Figure 1). Nineteen children had developed a diffuse maculopapular rash. The laboratory profile of children with scrub typhus is illustrated in Table 2. Thrombocytopenia defined by a platelet count of less than 100×10^9/L of blood was striking in one-third of children. Of the 262 children, 25 children were found to have severe scrub typhus and 18 children required intensive care stay; nine required ventilator support for pneumonia, and six required neurocritical care monitoring for meningoencephalitis. Chest radiograph suggestive of bronchopneumonia was noted in 11 children, and hemophagocytic lymphohistiocytosis was identified in three children (Table 3). There was no mortality during the study period. Multivariate analysis revealed elevated aspartate aminotransferase as a significant predictor of severity of scrub typhus ([OR 3.9], *P* value 0.005). Other variables such as fever > 5 days, eschar, leukocytosis, thrombocytopenia, hypoalbuminemia, and hyponatremia were insignificant. Overall, 239 children received doxycycline therapy, and 23 received azithromycin therapy. Severe forms of scrub typhus with complications received a 14-day therapy. Rapid defervescence within 48 hours was noted in 87% of the children. Table 4 compares the profile of children based on eschar, a clinical hallmark of scrub typhus. Clinical evidence of lymphadenopathy was found to have a significant association with eschar in children with scrub typhus ($P < 0.005$).

DISCUSSION

In this 6-year retrospective study, the authors describe the profile of pediatric scrub typhus and share the single-center experience of one of the largest data in children from Indian subcontinent. IgM ELISA was used for the diagnosis of scrub typhus in our study. Weil Felix is the cheapest and the most easily available method for scrub typhus serological diagnosis and has been used hitherto in several studies. Its low sensitivity, dubious false positivity in *Proteus* infections and its utility only in the second week of illness are the major drawbacks and have been supplanted by other serological methods such as IgM ELISA, PCR, and indirect immunofluorescence assay. Indirect immunofluorescence assay is

TABLE 1
Clinical characteristics of 262 children with scrub typhus infection

Characteristic		Number	Percentage
Gender distribution	Male	170	64.9
	Female	62	23 0.6
Age distribution (years)	< 1	13	4.9
	1–5	152	58.1
	6–10	82	31.29
	11–14	15	5.7
Duration of fever (days)	< 3	19	7.2
	3–5	99	37.7
	> 5	144	54.9
Vomiting		79	30.2
Abdominal pain		33	12
Maculopapular rash		19	7.2
Generalized edema		37	14.12
Respiratory distress		12	4.5
Lymphadenopathy		245	93.5
	Generalized	217	82
	Localized	28	10.6
Eschar		83	31.6
	Interscapular area	4	4.8
	Wrist	1	1.2
	Leg	11	13.25
	Axilla	19	22.8
	Groin	20	24.09
	Ear lobe	6	7.22
	Trunk	8	9.6
	Neck	8	9.6
	Shoulder	2	2.4
	Eyelid	4	4.8
Jaundice		1	0.3
Hepatomegaly		185	70
Hepatosplenomegaly		87	33.2
Encephalopathy		6	2.3

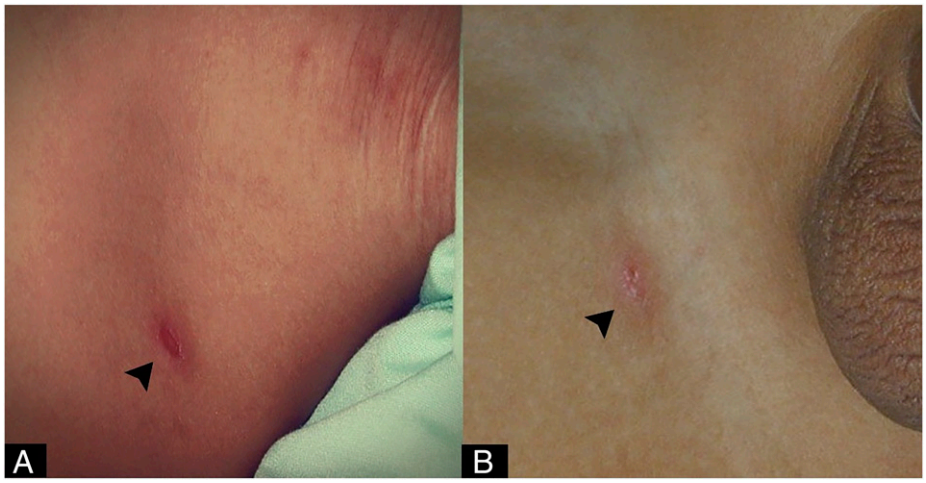

FIGURE 1. Well-established eschar in the axilla (**A**) and groin (**B**). This figure appears in color at www.ajtmh.org.

the gold standard test for diagnosis but is limited by expensive fluorescent microscopy and expert training.[4] IgM ELISA testing with optimal sensitivity (91%) and specificity (99%), like in our study, is the practical alternative in resource-limited settings.[7]

In our study, boys and children younger than 5 years were likely to be infected with scrub typhus, similar to that reported by Ganesh et al.[11] This could be justified by the increased outdoor play in the vector-ridden vegetation by children. In addition, 13 infants (5%) were diagnosed with scrub typhus. This is in consonance with studies by Dinesh et al. and Palanivel et al. who had described infantile onset scrub typhus in approximately 10% of their cohorts.[12,13] This comparatively higher percentage reported by the two authors might be due to the less number of children recruited in their study. Given the restricted outdoor activity in infants, Narayanasamy et al.[13] suggested the role of mite-ridden rodents or domesticated dogs in the transmission. However, a secondary route of exposure with mites hidden in garments brought in from outdoors is a reasonable explanation.[14]

Scrub typhus infection is the leading treatable cause of nonmalarial febrile illness in Asia. Over the last decade, it has become a seemingly ubiquitous part of Indian subcontinent with several published reports from distinct geographical locations. A review of the published literature on pediatric scrub typhus from India over the last decade was carried out by the authors[11–21](Table 5). For the purpose of this review, citations were identified through PubMed search limited to the past 10 years (2010–2019) using the search terms (including variations), "scrub typhus," "children," and "India," combined with study filters for cohort studies and original research. Acute undifferentiated fever lasting for more than 5 days with hepatomegaly and lymphadenopathy is one of the compatible clinical features of scrub typhus infection and has been reiterated from our analysis. However, in areas of high endemicity such as India, the threshold for diagnosis has to be lowered, as exemplified from our study, where 44% of children were identified within the first 5 days.

Although eschar is indicative of scrub typhus infection, its absence does not rule out the disease. The prevalence of eschar is extremely variable, ranging from < 1 to 92% in the

TABLE 2
Laboratory profile of 262 children with scrub typhus infection

Laboratory parameter	Cutoff	Number	Percentage
Thrombocytopenia (×109/L)	< 100	83	31.6
	< 50	10	12
	> 50	73	87
Total leukocyte count (mL)	< 4,000	48	18.3
	4,000–11,000	169	64.5
	> 11,000	45	17.1
Anemia		76	29
	< 1 years	3	3.6
	1–5 years	40	53.2
	5–10 years	27	35.3
	> 11 years	6	7.9
Raised liver enzymes (> 120 IU/L)	AST	69	26
	ALT	47	18
Hyponatremia	< 135 meq/L	43	16.5
Hypoalbuminemia	< 3.5 g/dL	39	14.8
Erythrocyte sedimentation rate	> 30 mm/hour	23	8.7
Total bilirubin	> 2 mg/dL	1	0.3
Chest X-ray	Bronchopneumonia	11	4.1
Echocardiography	Left ventricular dysfunction	1	0.3
Neuroimaging	Contrast enhancement	3	1
IgM ELISA scrub typhus	> 0.5 OD	262	100

AST = aspartate aminotransferase; ALT = alanine aminotransferase; OD = optical density; IU/L = international units per litre.

TABLE 3
Clinical profile of 25 children with severe form of scrub typhus infection

Characteristic		Number	Percentage
Median age, years (IQR)		4 (1–9)	
Male		15	60
Duration of fever (days)	< 3	4	16
	3–5	7	28
	> 5	14	56
Median duration of fever, days (IQR)		7 (3.5–7.5)	
Complications			
Bronchopneumonia		11	4
Acute respiratory distress syndrome		2	0.7
Meningoencephalitis		6	2.3
Acute kidney injury		2	0.7
Hemophagocytic lymphohistiocytosis		3	1
Myocarditis		1	0.3

IQR = interquartile range.

available literature.[22–24] It was noted in 31% of the children in our study. Eschar is highly evolving and develops at the site of mite bite; it initially begins as a central vesicle with surrounding erythema and overlaying scales and finally heals as necrotic lesion resembling a burn of a cigarette toward the end of the first week.[25] Dark skin tone, uncharacteristic manifestations of eschar, and concealed areas of the body like groin, axillary skin folds, and behind ear lobule are few of the challenges in clinical examination. We compared the clinical features of children with scrub typhus based on the eschar and found a significant association between clinical evidence of lymphadenopathy and eschar positivity. Accordingly, lymphadenopathy may be considered as a clinical pointer toward eschar, and a detailed serial examination is warranted. Also, clinical identification of eschar has diagnostic implications: PCR testing of the eschar swabbing is a rapid and reliable bedside tool in the early phase of the disease.[26,27]

Scrub typhus is, in general, a simple febrile illness with admirable outcome if treated early, as evidenced by nil mortality in our 262 children. This is in concordance with previous studies from India where mortality rates predominantly ranged from 0% to 7.5%. Furthermore, only 25 children (9.5%) from our study developed severe forms of scrub typhus marked by organ dysfunction. This is remarkably low when compared with earlier studies from the same region. Manish et al.[18] demonstrated an exceedingly high complication rate following scrub typhus infection with high incidences of myocarditis (34%) and acute kidney injury (20%) in their cohort of 35 children.Rarity of the disease in the region, which is not a hilly area, low index of suspicion for early diagnosis in 2011 when the study was conducted, and their small sample size can explain the high complication rate noted by Manish et al. Our results, however, are comparable with the study of 358 children from Chennai, 150 km from our center, by Ganesh et al.[11] who reported a 14.5% complication rate. Furthermore, Ganesh et al. identified elevated aspartate aminotransferase liver enzyme levels and thrombocytopenia as predictors of complication due to scrub typhus. An elevated aspartate aminotransferase liver enzyme level as a determinant of severe scrub typhus has been re-established by our study. Intrahepatic sinusoidal endothelial vasculitis and direct cytopathic liver damage contribute to this elevation. Unexplained transaminitis without jaundice in a febrile child should raise the suspicion for scrub typhus infection in endemic areas.[28] Other predictors of severe scrub typhus such as hypoalbuminemia, hyponatremia, encephalopathy, and leukocytosis proposed by Narayananasamy et al.[29] were not recognized in our study.

Likewise, three children developed hemophagocytic lymphohistiocytosis following scrub typhus in our cohort. Pancytopenia and hyperferritinemia hinted at the diagnosis and intravenous azithromycin without chemotherapy was effective. Data on hemophagocytic lymphohistiocytosis, as a life-

TABLE 4
Comparison of clinical and laboratory profile of children with scrub typhus based on eschar positivity

Parameter	Eschar present (*N* = 83)	Eschar absent (*N* = 179)	*P*-value
Mean age (years)	5	5	
Gender			
Male	47 (56.6%)	123 (68.7%)	0.077
Female	36 (43.3%)	56 (31.2%)	
Clinical profile			
Fever < 5 days	30 (36.1%)	88 (49.1%)	0.066
Fever > 5 days	53 (63.8%)	91 (50.8%)	
Vomiting	25 (30.1%)	54 (30.1%)	0.792
Abdominal pain	6 (7.2%)	27 (15%)	0.877
Jaundice	1 (1.2%)	0	–
Maculopapular rash	12 (14.4%)	7 (3.9%)	0.95
Edema	22 (26.5%)	15 (8.3%)	0.061
Respiratory distress	3 (3.6%)	9 (5%)	0.088
Encephalopathy	3 (3.6%)	3 (1.67%)	0.796
Lymphadenopathy	82 (98.7%)	163 (91%)	0.0381
Hepatomegaly	63 (75.9%)	122 (68.1%)	0.253
Splenomegaly	34 (40.9%)	53 (29.6%)	0.095
Laboratory profile			
Anemia	27 (32.5%)	49 (27.3%)	0.473
Leukopenia	14 (31.3%)	34 (25.6%)	0.416
Thrombocytopenia	31 (37.3%)	52 (29%)	0.229
Raised AST	25 (30.1%)	44 (24.5%)	0.419
Raised ALT	15 (18%)	32 (18%)	0.512
Hyponatremia	17 (20%)	26 (14.5%)	0.452
Hypoalbuminemia	16 (19%)	23 (13%)	0.482
Raised ESR	7 (8.4%)	16 (9%)	0.687

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ESR = erythrocyte sedimentation rate.

TABLE 5

Analysis of the clinical profile and outcome of pediatric scrub typhus infection from India during 2010–2019

	Rashna[15]	Palanivel[12]	Manish[18]	Krishna[16]	Kalal[19]	Bhat[20]	Dinesh[13]	Masand[21]	Ganesh[11]	Basu[14]	Bal[17]	Our study
Sample size	24	67	35	52	53	66	117	30	358	61	201	262
Place of study	Shillong	Chennai	Pondicherry	Chennai	Bengaluru	Dehradun	Pondicherry	Rajasthan	Chennai	Kolkata	Odisha	Pondicherry
Year of publication	2011	2012	2012	2015	2016	2016	2016	2016	2018	2019	2019	2020
Mean age (years)	9.4	NA	6.3	NA	7.3	8.8	6.5	8.5	NA	6	5.4	5 years
Age range	NA	2m-NA	1.5–12	7m-16	NA	8m-18	6m-12	3–16	1d-18	1.5–12	NA	7 m-12
Male (%)	54	44	60	57	71	59	50	70	59	53	62	65
Fever > 5 days (%)	100	NA	83	96	NA	> 73	100	82	100	100	100	55
Eschar (%)	42	46	11	67	NA	20	42	3	67	49	18	32
Hepatomegaly (%)	33	98	91	94	67	82	70	NA	94	NA	NA	70
Splenomegaly (%)	46	88	60	73	32	59	54	NA	90	NA	NA	40
Lymphadenopathy (%)	12.5	60	37	15	49	38	35	NA	25	59	74	93.5
Hepatosplenomegaly (%)	NA	NA	NA	NA	NA	NA	NA	60	NA	52	33	33
Edema (%)	NA	52	60	50	24.5	39	21	NA	48	52	22	14
Encephalopathy (%)	17	58	23	7	17	23	25	NA	NA	34	NA	2.3
Laboratory diagnosis	WF	ELISA	WF	ELISA	ELISA	ELISA	ELISA	ELISA	ELISA	WF/ELISA	ELISA	ELISA
Anemia (%)	NA	83	NA	NA	70	62	56	60	NA	83	54	29
Thrombocytopenia (%)	26	78	31	25	66	53	16	26	23	59	43	32
Hyponatremia (%)	66	12	17	46	9	NA	40	10	35.5	50	NA	16.5
Transaminitis (%)	58	65	31	62	81	61	48	60	38	30	73	44
Complications (%)	66	70	94	15	56	83	43	13	14.5	17	5.5	9.5
Mortality (%)	0	18	3	0	0	7.5	NA	6.6	0.8	1.6	0	0

NA = not available; WF = Weil Felix.

threatening complication of scrub typhus in children, are grossly deficient and limited to occasional case series. Jin et al.[30] reported the beneficial outcome in 15 children with scrub typhus associated HLH with intravenous antibiotics (azithromycin or chloramphenicol) without the need for 2004 HLH protocol chemotherapy.

Large sample size, robust back up of data from a single center, and analysis of predictors of severe scrub typhus are the strengths of the study. Our study has few limitations such as its retrospective design and evaluation of only hospitalized children with modest representation of the community.

In conclusion, our study accentuates the varied spectrum of tsutsugamushi infection in children including a 9.5% complication rate. Elevated aspartate aminotransferase enzyme levels is a predictor of severity. Meticulous examination for eschar is merited in children with lymphadenopathy. Zero mortality in our cohort signifies the excellent outcome with judicious first-line antibiotics.

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