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Seroprevalence and potential risk factors associated with severe scrub typhus infection: an experience from a tertiary care set up in Odisha, India

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ABSTRACT

Background: Scrub typhus a mite-borne disease is being reported across globe in increasing numbers in known endemic as well as non-endemic areas. Non-specific clinical manifestations make it one of the most underreported diseases.

Objectives: Owing to the lack of adequate prevalence data from our region, the present study aims to denote the prevalence of scrub typhus in Odisha and factors associated with development of various complications of this disease.

Material and Methods: All patients who were clinically suspected as scrub typhus during the study period of one year coming to our hospital were tested for IgM antibodies against *Orientia tsutsugamushi* by commercially available enzyme-linked immunosorbent assay (ELISA) kit. Other common endemic diseases were ruled out by appropriate tests. Clinical data for admitted patients were obtained from case sheets. The patient demographics, treatment and laboratory data of the complicated and uncomplicated scrub typhus cases were noted. Data was entered in excel sheet and tabulated by SPSS software.

Results: In the study among 2449 suspected cases, 398(16.3%) were positive for scrub typhus by IgM ELISA with peak incidence from August to November months. There was male preponderance of the illness with peak age of affection being 51-60 years. Eschar was noted only in 6 cases, and 49 cases went on to have various complications, commonest being meningoencephalitis. Mortality was very low in our study. Longer duration of fever before seeking treatment was significantly associated with development of complications.

Conclusion: The prevalence of scrub typhus was 16.3 % among the study population. Taking scrub typhus diagnostics to the peripheral level is the need of the hour to ensure early diagnosis and prevent severe disease.

Introduction

Scrub typhus is one of the important causes of acute febrile infectious illness globally. It is caused by bacteria named *Orientia tsutsugamushi,* other closely related species *Candidatus Orientia chuto*[1]and *Candidatus Orientia chiloensis*.[2] It is transmitted by mite bite particularly from that of chigger of *Leptotrombidium deliense* in India. It is one of the world's most underdiagnosed diseases and the burden of this disease is vastly underreported due to unavailability of adequate testing facilities, scarce

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research and non-distinctive clinical manifestations.

Every year about 1 million infected cases of scrub typhus are reported globally with mortality of around 30% when not treated.[3] The cases of scrub typhus in India is increasing steadily since past years and it is being detected outside the previous catchment areas. This is probably attributed to climate change and incessant travelling.

The present study aims to update the knowledge of prevalence of scrub typhus in our area and denote the significant risk factors associated with severe scrub typhus.

Materials and methods

Study setting

Present study was designed as a retrospective study from September 2023 to August 2024 in our tertiary care teaching hospital in Bhubaneswar, Odisha, India. This is a 1400-bedded hospital which caters mostly to the middle and lower socioeconomic status patients of the state. Odisha is a coastal state located in the eastern part of India. The weather is humid for most of the months of the year and receives rainfall from mid-June to September and is pleasant to humid in winter months between December and March.

Sample collection

All patients who were suspected during the study period of having scrub typhus and were sent for IgM ELISA (Scrub Typhus Detect™ IgM ELISA system, InBios International Inc.) for *Orientia tsustugamushi* to the central laboratory of our hospital were considered for the study. Central laboratory of the hospital receives samples from all the outpatient departments, wards and ICUs of the hospital and test are performed in house. The IgM ELISA is performed on the serum sample of the patients as per manufacturers' instructions and quality control measures are taken care of for each run of the ELISA test.

Suspected case was defined as a patient having fever ≥5 days without any other etiology with/without eschar. Possible case was defined as a suspected case with OD>0.5 for IgM by ELISA. Confirmed case is a possible case which showed effervescence on treatment with doxycycline/ azithromycin.

Patient data was collected from the lab register of the central laboratory and was used for finding the prevalence of the disease. Clinical data of the patients were extracted from the case sheets obtained from the medical record department for the possible scrub typhus patients admitted into wards or ICU and data was noted in a predesigned Performa. All these patients were evaluated for the demographics, clinical features, course in the hospital, laboratory parameters, treatment and various complications were carefully noted. Data for basic laboratory tests like complete blood count, renal function tests (blood urea and serum creatinine), blood glucose, and liver function tests serum bilirubin (direct and indirect), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) was noted.

Exclusion criteria

Patients where tests for malaria, typhoid fever, dengue, leptospirosis, and pneumonia were positive and those where the cause of fever was known as any chronic illnesses, HIV or malignancy were excluded from the study.

Data thus obtained was entered in MS excel and analysis was done for various parameters. Qualitative variables were presented as frequency while quantitative variables were denoted with mean±SD. Associations was determined by using Chi-square test or Fisher's exact test. Univariate and multivariate regression analysis was performed for the independent predictors of severity. The $p<0.005$ was considered as significant. All the statistics were done using SPSS software version 22.0 (SPSS Inc., Chicago, IL).

The study was approved by the Ethics Committee of the hospital via Ref.no/IEC/IMS.SH/SOA/2O23/523. Dt- 2.5.23. The participant information was kept confidential. Because of the retrospective nature of the study, the diagnostic and treatment of the patients was not interfered in any way.

Results

Prevalence of scrub typhus

During the study period total 2449, clinically suspected cases were received in the lab from which 398 (16.3%) samples were positive by IgM ELISA taking a cut off OD of 0.5**.** Among this 339 (85.2%) were adults and 59 (14.8%) belonged to pediatric population of less than14 years. Mean and SD of the cut off OD of the cases was 2.13±1.64 (Figure 1).

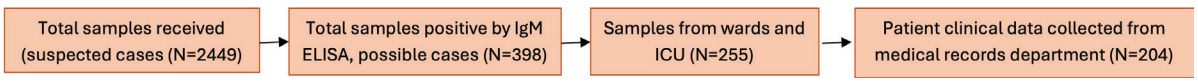

Figure 1. *Summary of the samples the study.*

Spatio-temporal distribution of cases

Scrub typhus cases are spread across the year except for winter months of December, January and February in our area. A rise in the number of cases from August was noted with peak incidence in November (Figure 2).

Similarly, the samples were mostly from Eastern part and the northern part of the state distributed across various districts as denoted in Figure 3.

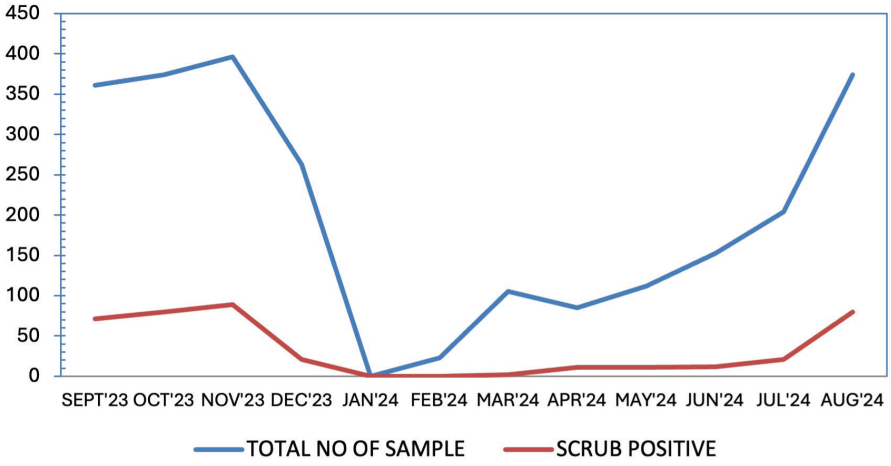

Figure 2. *Temporal distribution of scrub typhus cases in the study.*

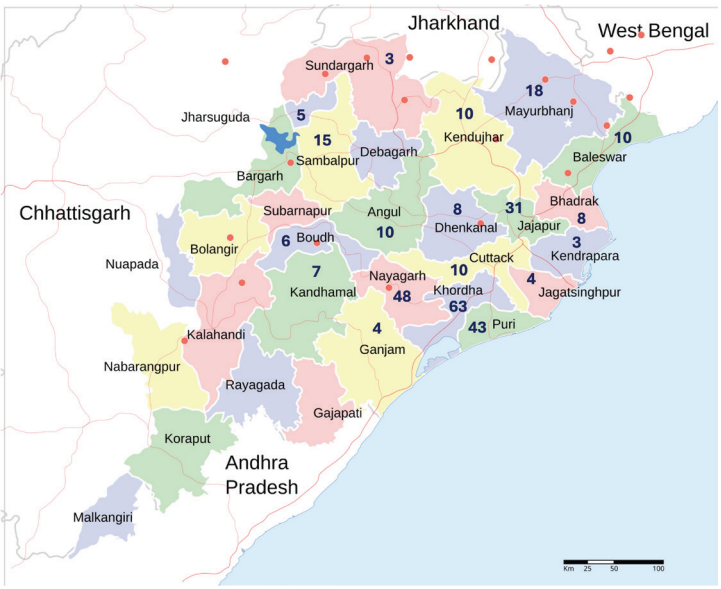

Figure 3. *Distribution of cases in the state.*

The samples were from Khordha (15.8%), Puri (10.8%), Nayagarh (12.1%) and Jajpur (7.8%) districts. The Southern and western districts of the state had a very little representation in our patient data.

Demographics of the patients

Among the total positives included (204) 64.4% were males. Mean age of patients was 35.5±23 years and median age being 35 years. The commonest age group of afflictions of the patients was 51-60 (19.8 %) years followed by 31-40 (15.5%), 41-50 (15.8 %) and 71-80 (18.5%) years.

Presenting symptoms

Fever was the most common presenting illness seen in 94.6% of patients. 65.8% of these patients presented to the hospital after 5 days fever. Mean duration of fever before presentation to the hospital was 8.4±6.8 days. Chill rigor was associated in 37.8% of cases. Other nonspecific presenting features were headache (27.9 %) and weakness (28.9%). Pain of the abdomen was noticed in about 38 % of patients while respiratory symptoms with breathlessness and cough were seen in 22.5 % and 35.8% cases respectively. Sensorial alteration was the presenting complaint in 25.5 % cases (Table1). Mean duration of the hospital stay in the scrub typhus cases in our set up was

7.29±5.5 days median being 6 days. ICU stay was noted in 49 (24.01%) patients and mean duration of ICU stay was 1.01±2.1 days. Mortality was seen in 2(0.9 %) of cases. Among the total cases (204), 49 (24.01%) progressed to complicated or severe scrub typhus. Some patients developed more than one complication or organ system affection. The various complications are summarized in Table 2.

Table1. Different presenting symptom of the cases (N=204).

Symptom	Number (% total)	Complicated scrub typhus patients (% total)	Uncomplicated scrub typhus patients (% total)
Fever	193 (94.6)	98	97
Fever <5 days	66 (34.2)	30.6	33
Fever >5 days	127 (65.8)	69.4	64
Chill and rigor	73 (37.8)	69.4	45
Headache	57 (27.9)	20.4	28
Weakness	59 (28.9)	14.2	29
Joint pain	24 (11.8)	4.08	12
Breathlessness	46 (22.5)	26.5	15
Cough	73 (35.8)	36.7	37
Pain abdomen	77 (37.8)	2.9	38.1
Diarrhea	45 (22.1)	28.6	19
Vomiting	81 (39.7)	1.5	37
Altered sensorium	52 (25.5)	23	18.4
Eschar	8 (3.92)	6.1	6
Hepatomegaly	16 (7.8)	16.3	9
Splenomegaly	23 (11.3)	22.4	12

Table 2. Various complications encountered in severe scrub typhus cases in the study.

Complication	Number (%)
Pneumonia	4 (8.1)
Acute kidney Injury	7 (14.2)
Anemia	1 (2.0)
Thrombocytopenia	1 (2.0)
Meningoencephalitis	14 (28.5)
Shock	12 (24.5)
Acute respiratory distress syndrome	4 (8.2)
Dyselectrolytemia	8 (16.3)
Myocarditis	2 (4.1)
GI bleeding	1 (2.0)
Hepatitis	6 (12.2)
MODS	3 (6.1)

Fever was the commonest symptom in the scrub typhus patients. While weakness, myalgia or flu like illness was the predominant picture in uncomplicated cases, severe cases presented with chill rigor. Other features like shortness of breath; diarrhea was seen more often in complicated cases. The uncomplicated cases had cough with pain abdomen and vomiting (Table1).

The demographic data of severe and uncomplicated scrub typhus cases are compared in Table 3 and 4. There is no significant difference in the mean age and sex distribution of the severe and uncomplicated scrub patients. The duration of illness before seeking health care was significantly higher in severe scrub cases than their counterpart. The severe cases had higher association with diabetes mellitus and hypertension as co-morbidities. ICU stays and the duration was significantly higher in severe cases than uncomplicated ones.

Among laboratory parameters, liver enzymes SGOT and SGPT was raised in significant number of uncomplicated and severe scrub typhus patients (89, 79.6 for OT; 78, 73.4% for PT) respectively. Total bilirubin was raised in 23%, 97.9 % of uncomplicated and severe cases respectively while Alkaline phosphatase was raised to more than 140 IU in 30% and 34.7% respectively. Platelets less than 1 lakh/ were seen in 31% and 30.6 % of uncomplicated and severe scrub cases.

Table 3. Demographic, clinical characteristics and laboratory findings on admission of the patients.

	Severe scrub typhus	Uncomplicated scrub typhus
Demographic of the patients		
Age>60 (Mean±SD)	36.5±24.04	34.8±23.1
Male:Female	1.45	2.13
Duration of illness before admission	8.5±5.6	8.4±7.2
Length of hospitalization (Mean±SD)	7.7±3.2	6.7±5.8
Mean duration from disease onset to effective antibiotic therapy (days)	9.73±5.8	10.23±3.7
Mortality (% total)	2 (4.08%)	0 (0)
Underlying diseases		
Diabetes mellitus (%)	20.4	8
Hypertension (%)	10.2	7
Liver ailments (%)	0	0
Lung disease (%)	0	0
Alcoholism (%)	8.2	1
Chronic kidney diseases (%)	2.04	1
Heart disease (%)	0	1
Sickle cell disease (%)	0	2
ICU stay (%)	44.9	12
Duration of ICU stay in days (Mean±SD)	2.08±2.9	0.49±1.35
Mortality (%)	2	0
Eschar (%)	4.08	6
Laboratory data		
Haemoglobin (gm/dL)	10.2±1.8	10.2±1.9
Total leukocyte count (x10^3/ mm^3)		8.8±5.8
Total platelet count (x10^5/mm^3)	2.3±6.8	1.9±1.9
Total bilirubin (mg/dL)	4.2±15.	1.4±1.86
Direct bilirubin (mg/dL)	2.23±14.9	1.75±10.2
SGOT(IU)	95.2±53.7	125.6±290.5

Table 3. Demographic, clinical characteristics and laboratory findings on admission of the patients. (Continue)

	Severe scrub typhus	Uncomplicated scrub typhus
SGPT (IU)	96.7±97	107.6±205.4
ALP(IU/L)	147.7±105.2	126.5±118.9
Urea (mg/dL)	44.9±44.7	26.2±24.5
Creatinine (mg/dL)	2.33±6.8	4.7±15.2
Mean OD	2.02±0.9	1.92±1.25

Table 4. Unadjusted relative risk and p value for selected factors on severe scrub typhus.

	Severe scrub typhus	Uncomplicated scrub typhus	Odds ratio	*p* value
Demographic of the patients				
Age (Mean±SD)>60	17	32	1.03	0.681
Male:Female	29:20	107:48		0.235
Duration of illness before admission	8.5±5.6	8.4±7.2	1.31	<0.001
Length of hospitalization (Mean±SD)	7.7±3.2	6.7±5.8	1.037	0.274
Mean duration from disease onset to effective antibiotic therapy (days)	9.73±5.8	10.23±3.7	1.02	0.32
Underlying diseases (diabetes, liver cirrhosis, COPD)	38.8%	18%	1.365	0.036
ICU stay (%)	44.9	12	1.569	<0.001
Duration of ICU stay in days (Mean±SD)	2.08±2.9	0.49±1.35	1.457	<0.001
Eschar (%)	4.08	6	0.236	0.569
Laboratory data				
Hb (<10gm/dL)	7	47	0.995	0.955
TLC (>10.0 x10^3/mm^3)	6	30	1.001	0.162
TPC (<1x10^5/mm^3)	4	0	1.024	0.540
Total bilirubin (>1.0 mg/dL)	5	47	1.092	0.083
Direct bilirubin (>0.2 mg/dL)	8	78	1.010	0.482
SGOT>40 IU	13	90	0.997	0.179
SGPT>40 IU	12	78	0.999	0.507
ALP (>200 U/L)	4	19	1.002	0.291
Urea (>24 mg/dL)	11	34	2.018	0.001
Creatinine (>1.4 mg/dL)	4	22	0.940	0.121

Discussion

A recent sero-epidemiological data showed that global pooled prevalence rate of scrub typhus in acute febrile illness was 24.93% [4] and that in Asia is 22.2%.[5] There has been a significant increase in sero-prevalence of scrub typhus since 2010 and it is estimated to be about 30% in community set up in India.[6] The epidemiology of scrub typhus varies as per change in climatic conditions and arthropod vector involved in transmission.[7,8] In India southern (55.5%)

and northern (31.5%) parts bear the major brunt of cases but, Eastern Indian literature is nominal.[6] In our study the prevalence of scrub typhus in clinically suspected cases was 16.3% similar to few other studies from Eastern India.[9] Increased travel have expanded the reach of scrub typhus into previously unreported areas for scrub typhus.[10] July to December months which correspond with monsoon and post-monsoon seasons correspond to high occurrences of scrub typhus cases in most of the states of India as in our case.[9,11-13]

Eschar is uncommon (9.5%-45%) in patients from Southeast Asia and Indian subcontinent,[14,15] probably due to presence in areas of tight fitted clothing as well as dark complexion in Indian set up making their elucidation difficult. Absence of eschar is an independent predictive factor for fatal outcomes.[16] But, in the present study eschar was detected in 3.9% cases with no significant difference of its presence among severe and uncomplicated cases. Variation in prevalence of eschar is because of different infecting *O. tsutsugamushi* strains[17,18] and vary across different ethnic populations.[19,20]

Most cases of scrub typhus in India are confined to young adults probably due to occupational or recreational exposure to mite infested vegetation and the median age of affliction is 28.1 years.[6]Predominant age group affected in our study was higher of >30 years age. Studies from countries like Japan also report 62% of scrub positive cases to be under 51-75 age group.[24] In the study by Liu et al. the highest number of cases (21%) were in the age group of 41-50 years.[22] Males constituted 64% of cases which agreed with previous studies by Liu *et al.* (56%) and Bal *et al.* (61.7%). [22,23] However, increased inclination of scrub typhus towards females was reported by studies carried out in few countries like South Korea.[24,25]

In our study hepatosplenomegaly was seen less often than other studies.[26] Splenomegaly is often not seen in dengue, thus helping to distinguish scrub typhus from dengue.[26] In our set up 24% cases developed various complications the most common being meningoencephalitis like other studies.[27,28] Meningoencephalitis is due to vasculitis caused by the organism. In scrub typhus CSF shows lymphocyte predominance cellular picture with increased protein levels. Other common complication was shock. We also found 2 cases of rare complication that is myocarditis in our study. The most common complication in scrub typhus in India in a review was hepatitis seen in 40.5% of scrub typhus cases[6] unlike in the present study. Raised liver enzymes (<3 fold) was nevertheless found in many patients in our study which never gave rise to severe scrub typhus.

Wang *et al*.reported the mortality of 6% in their review of various studies from India.[29] However, in our study, only 2 patients died of scrub typhus despite our patients being >30 years with about 20% belonging to age group of 51-60. Similar low mortality was also noted in another study.[30] Increased duration of illness before health care seeking was significantly different and was associated with higher odds of presenting with severe form of illness in our study. As expected, the severe cases had higher ICU admission and increased duration of stay in intensive care as well. In the present study initial hemoglobin, total platelet count or total leukocyte count and presence of underlying illnesses were not significantly associated with severity of infection.

Limitation

Present study has several limitations like genotypes or serotypes of *O. tsutsugamushi* have not been addressed and the samples were from a hospitalized setup in a single geographic region limiting its generalization.

Conclusion

The study highlights the growing prevalence of scrub typhus in endemic regions and its non-specific clinical manifestations. Although mortality can be averted by timely management, but complications can increase morbidity. The disease has heterogeneity in diagnostic methods, interpretation cutoff points, variable clinical presentation which thus points at further need for research.

Ethical approval

The study was approved by the ethics committee of the institute via letter no: Ref.no/IEC/IMS.SH/SOA/2O23/523. Dt- 2.5.23

Conflict of interest

None

CRedIT authorship contribution statement

Rout D: design, definition of intellectual contents, literature search, manuscript preparation, review, concepts and data acquisition; **PandaNR**: data analysis, statistics and manuscript editing; **Otta S:** design, definition of intellectual contents, literature search and manuscript preparation, manuscript editing, and manuscript review. All the authors have read and approved the final manuscript.

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