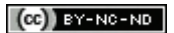


Presenting Features and Clinical Profile of Scrub Typhus Fever Cases in Adult Patients Admitted in a Tertiary Care Hospital in Puducherry, India

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ABSTRACT

Introduction: The infection of scrub typhus is caused by the bite of infected chiggers and the clinical manifestation of scrub typhus is characterised by the presence of fever, headache and body pain and rarely can cause rashes. There is paucity of information regarding the clinical presentation and the pathophysiological manifestation of scrub typhus infection, especially in tropical regions in Southern India.

Aim: To determine the clinical profile and manifestation of scrub typhus infection among adults in Puducherry, India.

Materials and Methods: This retrospective study was conducted on data of 79 IgM Immunochromatography (ICT) positive for scrub typhus patients, who were admitted and treated in 2015 in the study institution. Particulars regarding the clinical presentation, laboratory parameters and course in the hospital were documented from the medical records. Chi-square test was carried out to look for statistical significance between clinical and demographic parameters.

Results: Fever was the predominant symptom (49.4%) followed by headache (38%) and cough (19%). Eschar was present in 16.4% of the participants, and it was predominantly located in hypochondrium, anterior abdominal wall and sacral region (15.4%). About 17.7% of the participants had abnormal respiratory signs, of which bilateral crackles with ronchi was the most common sign (64.4%). While most common complication was gastrointestinal (18.1%); multi-organ involvement was present in 11.4% of the participants. Participants >40 years of age increasingly presented with symptoms of Central Nervous System compared to younger age group ($p < 0.05$).

Conclusion: The features of febrile illness with low total count and thrombocytopenia with high index of suspicion for scrub typhus may prevent mortality due to multiorgan failure by early institution of treatment.

Keywords: Eschar, Multiorgan damage, Zoonotic disease

INTRODUCTION

Scrub typhus is a bacterial infection caused by *Orientia tsutsugamushi*. The infection of scrub typhus is caused by the bite of infected chiggers and the clinical manifestation of scrub typhus is characterised by the presence of fever, headache and body pain and rarely can cause rashes. Scrub typhus is mite borne rickettsiosis and is an endemic infection in Asia specific region and is said to affect about 1 billion people [1]. Although this zoonotic infectious disease is more prevalent in mite infested areas, human beings get in contact with these mites as a result of recreational, occupational or agricultural exposure. During the pre-antibiotic era, scrub typhus was considered a lethal disease and after the advent of several antibiotics, especially doxycycline, the infection is largely controlled.

Scrub typhus has been present in Southeast Asia since World War II, however, there has been a resurgence of the infection in India in the last few decades [2]. Although, scrub typhus is prevalent in Indian sub-continent there are very few evidences of its presence in other parts of the country especially in North and East India. There is a very low level of awareness regarding the scrub typhus infection among doctors and therefore the index of suspicion among the clinicians, especially private medical practitioners in rural areas is far lower for scrub typhus infections [3]. There are however many cases reported among the paediatric age group while very few cases are documented in the adult populations. In addition, studies have reported an overall mortality between 7 and 30% for scrub typhus which is fairly higher compared to other infections and zoonotic diseases [4].

Apart from the increased mortality, the scrub typhus infection is also associated with the high risk of complications namely multiorgan dysfunction. There are studies which have documented impairment of the nervous system and renal system but there are few cases which have documented multiorgan dysfunction as a consequence of acquired scrub typhus infection [5].

There is paucity of information regarding the clinical presentation and the pathophysiological manifestation of scrub typhus infection, especially in tropical regions in Southern India. Therefore, this study was carried out in order to substantiate the clinical manifestation of this infection so as to sensitise the primary clinicians regarding the scrub typhus infections. The significance of evaluating scrub typhus in tropical countries like India stems from the fact that the disease is widely distributed in the tsutsugamushi triangle which comprises of various countries in the Asia Pacific region including Japan, China, India, Pakistan, Afghanistan and southern parts of Russia [6]. This study was carried out to determine the clinical profile and manifestation of scrub typhus infection among rural adults in Puducherry, India.

MATERIALS AND METHODS

This Retrospective study was conducted in the Department of General Medicine in a tertiary care hospital from January 2015 to December 2015. The case records of all the adults who were admitted with scrub typhus infection during the study period were included in the study, after due approval from the institutional ethical board. All the procedure have been followed according to the Declaration of Helsinki.

Inclusion Criteria

Adult patients who were positive for IgM antibody for scrub by Immunochromatography (ICT).

Exclusion Criteria

Clinical confirmation of any other co-existing febrile illness like malaria, dengue or any other tropical diseases, children <18 years of age, case records with insufficient/incomplete medical data.

Sample Size and Sampling Technique

A total of 94 cases were recorded in the year 2015. Among the 94 cases, immunochromatography for IgM positivity was present in 86 cases. Out of the 86 cases, 7 cases were excluded due to incomplete data. Analysis was carried out on a total of 79 cases.

Data Collection Tools

Data were collected from the medical records departments. The background profile regarding age and sex of the individuals were documented. The clinical presentation, physical examination and laboratory parameters were documented. The course in the hospital in terms of the duration of hospital stay, treatment given and patient outcomes were also documented.

STATISTICAL ANALYSIS

Data were entered and analysed using SPSS version 15.0 software. The clinical presentation was expressed in terms of presentations. Chi-square test was used to analyse the statistical significance of demographic characteristics with clinical manifestations. Independent sample t-test was used to determine the association between the means of the parameters and the clinical manifestation. A p-value <0.05 was considered statistically significant.

RESULTS

This study was carried out among 79 hospital admissions. Majority of the participants were males (60.8%) and were less than 40 years of age (55.7%). Fever was the predominant symptom (49.4%) followed by headache (38%) and cough (19%) [Table/Fig-1].

Characteristics	Frequency (N=79)	Percentage (%)
Primary symptoms*		
Fever	39	49.4
Headache	30	38.0
Cough	15	19.0
Generalised body pain	15	19.0
Breathlessness	29	36.7
Other symptoms*		
Ulcer	17	21.5
CNS symptoms	16	20.3
Swelling of feet	1	1.3
Joint pain	2	2.5
Tinnitus	1	1.3
Jaundice	2	2.5
Abdominal symptoms		
Present	30	38.0
Absent	49	62.0
Type of abdominal symptoms (n=30)		
Nausea	8	26.7
Vomiting	5	16.7
Loose stools	7	23.3
Abdominal distension	1	3.3
Pain abdomen	7	10.1
Epigastric pain	1	3.3
Malena	1	3.3

[Table/Fig-1]: Clinical symptoms.

*the figures will not total to 100

Almost all the participants had clinical hyperthermia (98.7%), about 17.7% of the participants had abnormal respiratory signs, splenomegaly was present in 12.7% of the participants [Table/Fig-2].

S. No.	Parameter	Frequency	Percentage
1 Vital signs			
	Tachycardia	36	45.6
	Hypertension	7	8.9
	Fever	78	98.7
	Tachypnea	1	1.3
2 General examination			
	Pallor	18	22.8
	Icterus	2	2.5
	Pedal oedema	2	2.5
	Lymphadenopathy	7	8.9
	Eschar	13	16.4
2.1 Eschar location (n=13)			
	Left axilla	1	7.7
	Right hypochondrial region	2	15.4
	Right elbow	1	7.7
	Right axilla	1	7.7
	Left hypochondrium	2	15.4
	Anterior abdominal wall	2	15.4
	Sacral region	2	15.4
	Left inguinal region	1	7.7
	Right iliac fossa	1	7.6
3 Systemic examination			
	Abnormal signs of cardiovascular system	0	0
	Abnormal signs of respiratory system (RS)	14	17.7
3.1 Specific respiratory system signs (n=14)			
	Bilateral crackles and rhonchi	9	64.4
	Bilateral wheeze present	3	21.4
	Right lower zone pneumonia	1	7.1
	Bilateral crepitations and right side pleural effusion	1	7.1
3.2 Specific abdomen signs			
	Hepatomegaly	7	8.9
	Splenomegaly	10	12.7
3.3 Specific signs of Central Nervous System (CNS)			
	Agitate and restless	3	50.0
	Features suggestive of meningo-encephalitis	1	16.6
	Auditory hallucination	1	16.7
	Drowsy	1	16.7

[Table/Fig-2]: Clinical findings.

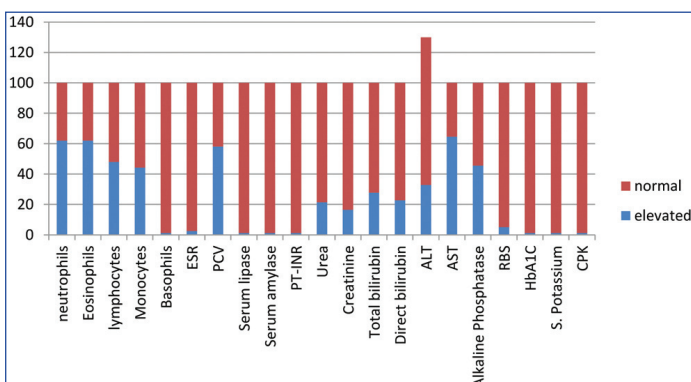
Among the study participants, low total white blood cell counts were seen in 63.3% and elevated total white blood cell counts were seen in 17.7% of the participants, while thrombocytopenia was present in 49.4%. Abnormal urine analysis was seen in 3.8% of the participants. About 44.3% of the participants have urine albumin in traces. Chest radiograph was largely normal and only one participant showed presence of bilateral nodular shadows [Table/Fig-3].

The distribution of laboratory parameters are shown in [Table/Fig-4]. The predominant parameters that were elevated were differential white blood cell counts and alkaline phosphatase levels. All the participants received doxycycline either alone (96.2%) or in combination with ceftriaxone or azithromycin. Majority of the participants were discharged within 6 days (48%), with a mean duration of hospitalisation of 5.6 days while 27.9% of the patients had complications. While most common complication was gastrointestinal (18.1%), multiorgan involvement was present in 11.4% of the participants [Table/Fig-5]. The mean values of various laboratory parameters estimated are given in [Table/Fig-6].

Characteristics	Frequency (N=79)	Percentage (%)
Total count		
Low (<4000 cells/cumm)	50	63.3
Normal (4000-11000 cells/cumm)	14	17.7
High (>11000 cells/cumm)	15	19.0
Platelet count		
Thrombocytopenia (<150,000 cells/mcL)	39	49.4
Normal (100,000-450,000 cells/mcL)	40	50.6
Urine analysis*		
Abnormal	3	3.8
Normal	76	96.2
Arterial Blood Gas (ABG)		
Abnormal	1	1.3
Normal	78	98.7
Chest radiograph		
Bilateral nodular shadows	1	1.3
Normal	78	98.7

[Table/Fig-3]: Laboratory findings.

*one or more of abnormal urine analysis including proteinuria, glucosuria, presence of pus cells, red blood cells



[Table/Fig-4]: Distribution of laboratory parameters.

This study found a significant difference in the presence of CNS symptoms with respect to the age of the participants. Participants aged >40 years were more at risk of CNS symptoms (31.4%) compared to those aged <40 years (11.4%). The observed difference was statistically significant ($p < 0.05$) [Table/Fig-7]. A significant difference in the total whole blood cell count was observed with respect to the sex of the participants. Females had increased risk of abnormal counts compared to males. The observed difference was statistically significant ($p < 0.05$) [Table/Fig-8]. There was also a significant difference in the laboratory parameters pertaining to renal functions, with respect to the presence of multi-organ involvement. The observed difference was statistically significant ($p < 0.05$) [Table/Fig-9]. However, there was no mortality among the study participants due to scrub typhus.

DISCUSSION

In this study majority of the participants belonged to less than 40 years of age. Another predominant symptom observed in our study was headache and apart from these symptoms, abdominal symptoms were also present in 38% of the participants. In a study done by Jain D et al., the mean age of the participants was 38 years, similar to this study. Abdominal symptoms were present in 33% of the participants, similar to this study (38%) [5]. In another study done by Narvencar KPS et al., the abdominal symptoms were present in 46.7% of the participants [7]. Eschar was present in 16.4% of the study participants, similar to the study observed by Zhang L et al., [8]. In addition 17.7% of the participants had respiratory signs including bilateral crackles. Moreover, splenomegaly was also present in 12.7% of the participants. Studies have documented that presence of eschar is essential in determining the prognosis of patients with scrub

Characteristic	Frequency	Percentage
Antibiotic used		
Cephotriaxone and doxycycline	1	1.3
Doxycycline and azithromycin	2	2.5
Doxycycline	76	96.2
Duration of hospitalisation (in days)		
>6	31	39.2
<6	48	60.8
Complication		
Yes	22	27.9
No	57	72.1
Types of complications (n=22)		
Gastrointestinal	4	18.1
Neuropsychiatric	1	4.5
Neuropsychiatric; electrolyte imbalance	1	4.5
Neurological	1	4.5
Gastrointestinal; haematological	2	9.1
Renal	3	13.6
Respiratory	2	9.6
Obstetric	1	4.5
Gastrointestinal; renal	1	4.5
Electrolyte imbalance	1	4.5
Renal; respiratory	1	4.5
Haematological; renal	1	4.5
Multi organ	1	4.5
Hepatic; renal	2	9.1
No of organs affected		
Single	13	16.4
Multi organ	9	11.4
No	57	72.2

[Table/Fig-5]: Course in the hospital.

Parameters	Mean	SD
Pulse (beats/minute)	85.3	9.4
Total count	7679.70	3372.6
Neutrophils	70.7	8.4
Lymphocytes	25.8	10.1
Eosinophils	1.4	1.4
Monocytes	2.4	1.4
Platelet count (lacs/cumm)	1.97	2.3
Haemoglobin (g/dL)	10.6	1.7
PCV	36.1	5.9
Urea (mg/dL)	31.0	26.8
Creatinine (mg/dL)	1.0	0.8
Total bilirubin	1.1	0.9
ALT	63.4	56.3
AST	62.8	53.0
ALP	98.2	40.8

[Table/Fig-6]: Mean values of the parameters.

Parameters	CNS		N (79)	Chi square	p-value
	Present	Absent			
Age (years)					
<40	5 (11.4)	39 (88.6)	44	4.8	0.02
>40	11 (31.4)	24 (68.6)	35		

[Table/Fig-7]: Association between demographic characteristics and significant symptoms.

Parameters	Total count			N (79)	Chi square	p-value
	Low	Normal	High			
Sex						
Female	23 (74.2)	1 (3.2)	7 (22.6)	31	7.3	0.02
Male	27 (56.3)	13 (27.1)	8 (16.7)	48		

[Table/Fig-8]: Association between demographic parameters and laboratory findings.

Factor	N=79	Mean	SD	t-value	95% CI	p-value
Urea	9	-0.396	0.527	-2.877	-0.670 to -0.122	0.005
Creatinine	8	1.375	0.517	-3.720	-0.762 to -0.230	0.0001

[Table/Fig-9]: Association between complication with multisystem involvement and clinical parameters.

typhus infections. Patients without eschar are proven for increased risk of severe complications. However, this correlation could not be explored in the index study due to paucity of information. Identification of preferences sites of eschar formation is also important in order to detect it early and address at earliest stages [9].

It is essential to document the incubation period and duration between onset of fever and the onset of other symptoms was clinically important. The incubation period is documented from time of bite by infected chiggers to appearance of fever. However, incubation period was not documented in the present study. In a study done by Takhar RP et al., three patients were diagnosed in the second week and had manifestation of fever and other manifestation of scrub typhus two weeks after the onset of fever [3]. However, several studies reported a variation in the presentation of eschar. Some Indian researchers like Vivekanandhan M et al., documented the prevalence of eschar to be around 45% [10]. It is worthwhile noting that the diagnosis made in the above study was using Weil-Felix reaction which does not have established validity. In the index study, we used rapid diagnostic test ICT which although is not a gold standard Test like immunofluorescent or Enzyme-Linked Immunosorbent Assay (ELISA) but is a good tool for rapid diagnosis [11].

Scrub typhus is predominantly said to result in multi organ dysfunction. With more participants having low leucocyte counts and significant prevalence of thrombocytopenia, 27.9% of participants had complications of which majority of the complications were related to gastro intestinal system including hepatomegaly and renal involvement.

However, multiple organs were affected in 11.4% of the present study participants. In another study 48.5% of the participants had more than three organ systems involve while 30% of the participants had about five organ dysfunctions during the hospital stay [3]. This difference could be due to the aggressive management and early presentation to the health care facility in index study; however, there is a need for substantial evidence to support the difference. The common complications involve circulatory collapse, Acute Respiratory Distress Syndrome (ARDS), haematological complications and electrolytes imbalances as seen in almost all participants in the study. Some studies have documented other extraneous complications including meningoencephalitis, gastrointestinal bleeding, acute renal failure, hearing impairment, opsoclonus and pancreatitis [3,12,13]. While most of the infections were easily controlled by doxycycline antibiotic, some of the patients required ceftriaxone and azithromycin combinations. Antimicrobial resistance was reported in several Asian countries like Thailand etc., [14]. Moreover, refractory cases have also been reported in other countries, with an emerging threat of drug resistance [15].

In this study, present authors found statistically significant relationship between the age of the participants and presence of CNS symptoms. There was an increase predisposition to CNS symptoms including lethargy etc., among patients who were >40 years of age compared to those <40 years of age. Moreover, there was a variation in total count levels with respect to the gender of the participants. Females were more prone for an increased variation while males were found to have near normal total count levels. There are few studies which have correlated the age and organ specific complications for scrub typhus.

We did not report any mortality from scrub typhus due to the presence of early case management and adequate antibiotic coverage. The mortality rate from scrub typhus has been ranging from 7-30% [16] all over the world with about 30% in Taiwan [17] and 10% in Korea [18]. In India studies done by Takhar RP et al., documented mortality rate of 21.2% [3]. It was higher compared to studies done by Mahajan SK et al., with the mortality of 14.2% and Kumar K et al., with the mortality of 17.2% [4,19]. The comparison with similar published studies is given in the [Table/Fig-10] [3,5,7,10,20-22].

Limitation(s)

Being a retrospective study the active burden of the infection in the population could not be ascertained. A long term follow-up study on

Study	Clinical symptoms		Clinical signs		Laboratory investigation	
	Parameters	Percentage (%)	Parameters	Percentage (%)	Parameters	Percentage (%)
Present study	Fever	49.4	Eschar	16.4	Raised serum creatinine	16.5
	Cough	19	Heptomegaly	8.9		
	Headache	38			Lymphadenopathy	8.9
	Abdominal symptoms	38				
	Multiple organs affected	11.4				
Girija S et al., [20]	Fever	100	Eschar	4	Elevated transaminases	20
	Chills	66	Heptomegaly	3	Thrombocytopenia	84
	Myalgia	95	Lymphadenopathy	4		
	Cough	40	Rash	3	Raised serum creatinine	80
	Nausea	28				
Inamdar S et al., [21]	Fever	79.5	Eschar	75.5	-	-
	Headache	97	Hepatomegaly	74		
	Abdominal pain	56	Lymphadenopathy	52.5		
	Anorexia	54.5				
Varghese GM et al., [22]	Fever	100	Eschar	55	Elevated transaminases	72.5
	Myalgia	32.4			Hyperbilirubinaemia	26.6
	Headache	42.8				
	Cough	37	Rash	1.2	Raised serum creatinine	12.9
	Altered sensorium	24.6				
	Seizures	6.5				

Vivekanandan M et al., [10]	Fever	100	Eschar	46	Elevated transaminases	95.9
	Myalgia	38	Hepatomegaly	28	Thrombocytopenia	28
	Headache	52	Lymphadenopathy	80	Hyperalbuminaemia	87.5
	Nausea	58	Rash	14	Hyperbilirubinaemia	20.5
	Cough	40	Altered sensorium	20	Raised serum creatinine	13
Jain D et al., [5]	Abdominal symptoms	33	Eschar	12.82	Thrombocytopenia	46.2
			Splenomegaly	51		
			Lymphadenopathy	20.5		
Narvencar KPS et al., [7]	Abdominal symptoms	46.7	Eschar	13.3	Raised serum creatinine	33.3
			Lymphadenopathy	26.7	Thrombocytopenia	40
Takhar RP et al., [3]	Fever	100	Eschar	12.1	Mortality rate	21.2
	Cough	48.5	Lymphadenopathy	18.2	Raised creatinine	51.5
	Myalgia	30.3				
	Multiple organ dysfunction	48				

[Table/Fig-10]: Comparison of clinical and laboratory findings of the present study with published literature [3,5,7,10,20-22].

large sample is required to analyse the clinical extent of involvement of the disease in order to devise preventive strategies.

CONCLUSION(S)

Scrub typhus is a common infection of the tropics and is often labelled as pyrexia of unknown origin. This study has documented the presence of significant correlation between age of the participants and clinical presentation of symptoms of central nervous system. This study also elucidated a significant association between age at presentation and symptoms of central nervous system. It is therefore essential to note that the index of suspicion should be high for scrub typhus fever when the patient presents with fever, thrombocytopenia and multi organ involvement in order to prevent mortality.

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