Original Research Article

Clinico-pathological profile of scrub typhus in children: a cross sectional study from Eastern India

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ABSTRACT

Background: Scrub typhus is a vector-borne zoonosis, endemic in Asia and it may present as an undifferentiated fever or with multisystem involvement. This study was carried out to understand the varied presentation of scrub typhus in children and the response to treatment in a tertiary care hospital in Eastern India.

Methods: All children between 1 month and 12 year of age admitted with fever for more than 5 days and positive IgM ELISA for scrub typhus were included in the study and their course in hospital was documented. They were randomly divided into 2 groups of 41 patients each, into doxycycline and azithromycin group and were then evaluated for therapeutic response.

Results: In this study, pallor (89%) was the commonest finding followed by hepato-splenomegaly (73.2%), pneumonia (65.9%) and rash was found in 43.9%. Eschar was found in 32.9% whereas serious complications like shock and meningoencephalitis was found in 9.8%. Pericardial effusion was detected in 23.2% cases, coronary artery dilatation in 11% cases and both effusion as well as coronary artery dilation was found in 2.4%. In azithromycin group, 73.2% patients had drug response whereas in doxycycline group, 92.7% patients had drug response and this association was statistically significant ($p=0.0188$). Two patients who presented late with shock expired but all others responded to treatment and were doing well on follow up.

Conclusions: Scrub typhus may present with multisystem involvement including cardiac manifestation which needs to be identified early by echocardiography. Doxycycline is still the best modality of treatment and if used early, outcome is favourable.

Keywords: Scrub typhus, Acute undifferentiated fever, Rickettsial infection, Eschar

INTRODUCTION

Scrub typhus is a rickettsial infection usually presenting with acute febrile illness along with multisystem involvement caused by *Orientia tsutsugamushi*.¹ It is a vector-borne zoonosis, endemic in South East Asia, the Pacific Islands and Northern Australia which is called the tsutsugamushi triangle, with reports of similar infections from Africa, the Middle East and South America.² This infection is transmitted to humans by the bite of infected chiggers (larvae) of trombiculid mites.³ There have been reports of sporadic outbreaks of scrub typhus mainly in

the Eastern and Southern Indian states with serological evidence of widespread prevalence of spotted fevers and scrub typhus, particularly during monsoon and post monsoon months.⁴⁻⁶

The pathogenesis of scrub typhus is uncertain. Recent studies suggest that the infection is stimulated by widespread infection of vascular endothelial cells, which correspond to the distribution of disseminated vasculitic and perivascular inflammatory lesions, observed in histopathological examinations. Vascular injury initiated by the infection is sustained by immune mediated

inflammation that together cause vascular leakage. The net result is significant vascular compromise and ensuing end organ injury, most often manifested in the brain and lungs.⁷ Scrub typhus without the eschar is a febrile illness without any evidence of localization and is hence termed acute undifferentiated fever. This illness is thus clinically indistinguishable from malaria, dengue fever, other rickettsioses, leptospirosis and enteric fever, which are common causes of acute undifferentiated fever in the Asia-Pacific region.⁸

Though there have been a number of reports of scrub typhus and other rickettsial infections, it is still grossly under-diagnosed because of their non-specific clinical presentation, low index of suspicion among clinicians and limited awareness about the disease and the complications.⁹⁻¹¹

Case definition of scrub typhus as per IAP guidelines

Suspected case

A patient having compatible clinical scenario, suggestive epidemiological features and absence of definite alternative diagnosis should be termed as a suspected case of rickettsia.

Probable case

Suspected case having either eschar or having rapid (<48 hours) defervescence with anti-rickettsial therapy or having suggestive laboratory features or having Weil-Felix test positive with titre of 1:80 or more in OX2, OX19 or OXK or positive IgM ELISA for rickettsia (optical density >0.5).

Confirmed case

Suspected case having rickettsial DNA detected in whole blood or tissue samples or four fold rise in antibody titres on acute and convalescent sera detected by immunofluorescence assay (IFA) or immunoperoxidase assay (IPA).

The clinical manifestations of scrub typhus can be varied and include non specific, most specific and systemic manifestations.

Non specific

High grade fever, malaise, headache, cough, generalised lymphadenopathy are the clinical manifestations of non-specific scrub typhus.

Most specific

Eschar which is almost diagnostic. The prevalence of an eschar is highly variable from 7 to 80 percent in various studies.

Systemic manifestations

These usually start towards the beginning of the second week which can be,

Cardiac:

Myocarditis, pericarditis, acute myocardial infarction are the cardiac manifestations.

Respiratory:

Pneumonia (atypical pneumonia with diffuse bilateral reticular infiltrations or focal consolidation) or pneumonitis, acute respiratory distress syndrome (ARDS) are the respiratory manifestations.

Neurological:

Meningitis/meningoencephalitis/encephalitis, acute disseminated encephalomyelitis, cerebrovascular accidents, cranial nerve palsies, parkinsonian/other movement disorders, cerebellitis, trigeminal neuralgia are the neurological manifestations.

Gastrointestinal

Acute abdomen, diarrhoea, vomiting, pancreatitis, gastrointestinal haemorrhage, splenic infarction, peritonitis/haemoperitoneum, liver dysfunction are the gastrointestinal manifestations.

Aims

This study was conducted in a tertiary care hospital in Eastern India to assess the varied clinical manifestations and laboratory parameters in patients with scrub typhus in the age group of 1 month to 12 years and to evaluate the drug response.

Objectives

The objectives were to evaluate the varied clinical presentations of scrub typhus in the age group of 1 month to 12 years, to perform spectrum of laboratory investigations with special emphasis on echocardiography, to assess drug response in terms of recovery between azithromycin and doxycycline group and to achieve follow up of the cases for any residual sequelae and demonstrate rise in titre of antibodies.

METHODS

The study design was a prospective cross-sectional study. The study was conducted from November 2018 to December 2019. Diagnosed patients of scrub typhus between 1 month to 12 years of age admitted in the department of paediatrics, Ramakrishna Mission Seva Pratishthan, Kolkata were the study population.

Method of collection of data

All children between 1 month and 12 years of age, admitted with fever for more than 5 days and positive IgM ELISA for scrub typhus were included in the study. These children were followed up during the hospital stay and their laboratory results, response to treatment and complications were documented. Initial investigation for malaria, dengue, UTI, pneumonia and enteric fever was negative. This study population was randomly divided into 2 groups of 41 patients each, into doxycycline and azithromycin group. They were then evaluated for therapeutic response in terms of defervescence of fever, resolution of symptoms as well as improvement of relevant echocardiographic findings. All patients were followed up for a period of 1 month to detect any residual disease.

Inclusion criteria

Children between 1 month to 12 years of age with persistent fever >5 days with OD value >0.5 for *O. tsutsugamushi* on IgM ELISA and Eschar (irrespective of duration of fever) were included in the study.

Exclusion criteria

Other causes of acute febrile illness such as malaria, dengue, leptospirosis, UTI, pneumonia and skin/soft tissue infections were excluded from the study.

Statistical analysis

Clinical and laboratory parameters of the patients and the significant factors were demonstrated using frequency table and appropriate chart/graphs. The vital and demographic factors of patient were evaluated using Chi square test or Fisher's exact test. Comparison between azithromycin or doxycycline for their performance was done using t test or Mann Whitney test, based on the nature of the dataset and subsequent results were tabulated with statistic value or p value. Any p value <0.05 was taken as significant. The statistical software used was SPSS v21.0.

Sample size

The sample size was calculated mainly based on the interest to test that azithromycin had non-inferior efficacy compared with doxycycline for the treatment of scrub typhus.

Assuming a 90% cure rate for doxycycline in both diseases, a relative difference of $\geq 10\%$ between the cure rates of the two groups was defined as non-equivalent. On the basis of a one-sided 0.05 significance level and 90% power, respectively, to reject the null hypothesis that the two treatments were not equivalent, testing of non-inferior efficacy required the sample size (N) based on the formula,

$$N=2 \times \left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{\delta_0} \right)^2 \times p \times (1 - p).$$

We obtained the sample size for each group be 41. Therefore total sample was 82.51.

Sample size of 82 patients of acute febrile illness serologically diagnosed as scrub typhus was taken.

Ethical clearance

Approval was taken from the institutional ethics committee before commencement of the study.

RESULTS

There were total 82 patients with serologically diagnosed scrub typhus (OD value >0.5 on IgM ELISA for *O. tsutsugamushi*). Table 1 shows the age distribution and clinical characteristics of these patients.

In this study pallor (89%) was the commonest finding followed by hepato-splenomegaly (73.2%), pneumonia (65.9%), rash in 43.9% and ascitis in 24.4% of cases. Eschar was found in 32.9% whereas serious complication like shock and meningoencephalitis was found in 9.8% of the cases (Table 1) (Figure 1).

Table 1: Age distribution and clinical characteristics of patients (N=82).

Clinical characteristics	Number (N=82)	Percentage
Age distribution		
1 month to 2 years	14	17
3 years to 5 years	35	42.6
6 years to 12 years	33	40.2
Eschar		
Present	27	32.9
Absent	55	67.1
Rash		
Present	36	43.9
Absent	46	56.1

Continued.

Clinical characteristics	Number (N=82)	Percentage
Pallor		
Present	73	89
Absent	9	11
Edema		
Present	22	26.8
Absent	60	73.2
Lymphadenopathy		
Present	52	63.4
Absent	30	36.6
Hepatosplenomegaly		
Present	60	73.2
Absent	22	26.8
Ascitis		
Present	20	24.4
Absent	62	75.6
Shock		
Present	8	9.8
Absent	74	90.2
Pneumonia		
Present	54	65.9
Absent	28	34.1
Meningoencephalitis		
Present	8	9.8
Absent	74	90.

Table 2: Laboratory parameters.

Laboratory parameters	Number	Percentage
Hb <11 gm/dl		
Present	74	90
Absent	8	10
Leucocytosis (WBC >15000 /mm³)		
Present	32	39
Absent	50	61
Thrombocytopenia (platelet <100,000 /mm³)		
Present	9	11
Absent	73	89
Raised CRP (>6 mg/l)		
Present	82	100
Hypoalbuminemia (alb <2.5 gm/dl)		
Present	23	28
Absent	59	72
Hyponatremia (Na <135 meq/l)		
Present	28	34.1
Absent	54	65.9
Transaminitis (raised AST, ALT)		
Present	56	68.3
Absent	26	31.7
Raised PT/INR		
Present	3	3.7
Absent	79	96.3
Azotemia (raised urea/creatinine)		
Present	11	13.4
Absent	71	86.6

Continued.

Laboratory parameters	Number	Percentage
Echo showing (pericardial effusion)		
Present	19	23.2
Absent	63	76.8
Echo showing coronary artery dilation		
Present	9	11
Absent	73	89
Echo showing (both effusion and CAD)		
Present	2	2.4
Absent	80	97.6

Table 3: Association between drug response and therapy.

Drug response	Azithromycin	Doxycycline	Total
No	11	3	14
Row (%)	78.6	21.4	100.0
Col (%)	26.8	7.3	17.1
Yes	30	38	68
Row (%)	44.1	55.9	100.0
Col (%)	73.2	92.7	82.9
Total	41	41	82
Row (%)	50.0	50.0	100.0
Col (%)	100.0	100.0	100.0

Chi square value: 5.5126; p value: 0.0188. odds ratio: 4.6444 (1.1880, 18.1577).

Table 4: Repeat echocardiogram.

Repeat echo after 2 weeks	Frequency	Percent
Normal	28	100.0
Total	28	100.0

Figure 1: Relative percentage of different clinical parameters.

Among the laboratory parameters, CRP was raised in all patients followed by anaemia in 90% of patients, raised transaminases in 68.3%, leucocytosis in 39%, hypoalbuminemia in 28% and hyponatremia in 34% of children. Thrombocytopenia was found in 11% of patients and altered PT/INR in 3.7% of cases. Renal failure was detected in 13.4% (Table 2) (Figure 2).

Figure 2: Relative percentages of different laboratory abnormalities.

In our study, 28 patients had some form of cardiac involvement out of which there was pericardial effusion in 19 (23.2%) cases, coronary artery dilatation in 9 (11%) cases and both effusion as well as coronary artery dilatation in 2 (2.4%) cases (Figure 3).

Regarding response to treatment, in azithromycin group, 30 out of 41 (73.2%) patients had drug response whereas

in doxycycline group, 38 out of 41 (92.7%) patients had drug response and this association was statistically significant ($p=0.0188$) (Table 3) (Figure 4).

On follow up, all 28 (100.0%) patients had normalisation of their echo abnormalities (Table 4).

Figure 3: Percentage of different echocardiographic abnormalities.

Figure 4: Response to therapy in the two groups.

DISCUSSION

Fever of more than 5 days duration was the inclusion criteria for enrolling the patients and the mean duration of fever in our study population was approximately 9 days. There were total 82 patients with serologically diagnosed scrub typhus (OD value >0.5 on IgM ELISA for *O. tsutsugamushi*). In a study by Kannan et al found that detecting *O. tsutsugamushi* specific IgM antibodies by ELISA have excellent sensitivity and specificity for the diagnosis of scrub typhus.¹² But a four-fold rise in the antibody level between the acute and convalescent sera is confirmatory. We found that 78 out of 82 patients demonstrated significant rise in the titre of antibodies by scrub IgM ELISA between acute and convalescent sera which is statistically significant ($p<0.05$).

There was a diversity of clinical manifestations such as Eschar (32.9%), rash (43.9%), pallor (89%), edema (26.3%), lymphadenopathy (63.4%), hepatosplenomegaly (73.2%), ascites (24.4%), shock (10%), pneumonia (65.9%), meningoencephalitis (10%) in our study

population. Lakshmanan et al (2018) found that scrub typhus is a common aetiology for an acute undifferentiated fever among children.¹³ In their study in 83 patients, gastrointestinal symptoms (76%) such as vomiting, diarrhoea and abdominal pain, lymphadenopathy (96%) and hepatosplenomegaly (61%) were common signs and symptoms and only six patients had severe illnesses. Out of these 83 patients, Eschar was seen in 50 (60%) patients.

In our study, we documented spectrum of laboratory abnormalities which were anaemia (90%), leucocytosis (39%), thrombocytopenia (11%), hyponatraemia (34%), hypoalbuminaemia (28%), raised transaminases (68.3%), altered coagulation profile (3.7%), renal failure in 13.4%, and CSF lymphocytic pleocytosis in 10%. Anaemia was the most common laboratory abnormality seen in 90% of patients, while CRP was raised in all the patients.

In a study by Khandelwal et al in 52 patients with scrub typhus, raised SGOT was seen in 49 (94.2%), raised SGPT in 41 (78.8%), thrombocytopenia in 46 (88.4%), leucopenia in 12 (23%) and leukocytosis in 11 (21.1%) patients.¹⁴ Common complication were hepatitis in 49 (94.2%), multi-organ dysfunction syndrome (MODS) in 12 (23.1%), ARDS and hypotension each in 10 (19.2%), meningoencephalitis in 5 (9.6%), acute kidney injury (AKI) in 3 (5.8%), hemophagocytic lymphohistiocytosis (HLH) and myocarditis in 1 (1.9%) patient each.

In a study by Narayanasamy et al 2018, in 230 children with scrub typhus, multivariate analysis identified 5 factors, breathlessness (OR: 6.85, 95% CI: 2.69 to 9.87), altered sensorium (OR: 11.48, 95% CI: 3.43 to 10.19), leucocytosis (OR: 3.38, 95% CI: 1.12 to 10.16), hypoalbuminemia (OR: 10.78, 95% CI: 2.66 to 48.76), and hyponatremia (OR: 10.08, 95% CI: 2.11 to 23.42) to be significantly associated with the severe scrub typhus cases.¹⁵

Patients who presented with poor prognostic factors such as leucocytosis, severe thrombocytopenia, hyponatraemia, hypoalbuminaemia, AKI, meningoencephalitis and shock had relatively delayed drug response and few did not respond to therapy as well. In our study, all the 8 patients who presented with shock (3 in doxycycline group and 5 in azithromycin group) did not respond to initial anti-rickettsial therapy and required additional broad spectrum antibiotics, fluid and inotropic support, ventilator support and 2 of them who had delayed presentation with refractory shock, expired.

Echocardiography (2D and M mode) was done in all the cases and we found that 19 (23.2%) patients developed pericardial effusion, 9 (11%) patients developed significant coronary artery dilatation and 2 (2.4%) patients developed both.

Interestingly repeat echocardiography done after 2 weeks showed normalization of the changes. In a study by Das

et al (2018) eleven out of forty three cases showed features of myocarditis requiring vasopressor and five cases showed long QT without progress to ventricular tachycardia.¹⁶

In our study, 82 patients were divided into 2 groups of 41 patients each. Out of these 82 patients, 68 (82.9%) patients showed favourable drug response to initial anti-rickettsial therapy. In azithromycin group, 30 (73.2%) patients responded while in doxycycline group, 38 (92.7%) patients responded. Association of drug response was statistically significant ($p=0.0188$). The 3 patients in doxycycline group who did not respond, presented with profound shock out of which 2 expired and 1 patient had concomitant positive blood culture for gram-negative septicaemia and required additional broad spectrum antibiotic coverage to show response.

Though various studies have now been published regarding the multisystem involvement in scrub typhus in children, this study showed the importance of echocardiography to establish a diagnosis of cardiac involvement, as pericardial effusion and coronary artery dilatation can often be missed clinically.

Limitations

The sample size was small and the rickettsial DNA in whole blood or tissue samples could not be done as it was not available. Also it was a hospital based study, so the results cannot be extrapolated to the community.

CONCLUSION

There can be a huge diversity in the range of clinical presentations of scrub typhus involving almost every organ system ranging from pneumonia, cardiac involvement, shock, meningoencephalitis or renal failure. This study emphasizes the need for routine echocardiographic screening of all patients of scrub typhus which can depict coronary artery dilatation and pericardial effusion, which can have prognostic and therapeutic implications. In our study, although response was achieved with both doxycycline and azithromycin, we found doxycycline to be superior to azithromycin in terms of therapeutic response.

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