Clinical spectrum of scrub typhus in Eastern India: A 3 year experience

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Abstract

***Introduction**:* Scrub typhus is a serious public health problem in Eastern India.

Objectives: To study the clinical spectrum and complications of scrub typhus and its doxycycline responsiveness.

***Method**:* This study was carried out over a 3 year period on 203 serologically confirmed scrub typhus cases in a tertiary care centre in Eastern India.

***Results**:* Fever (100%), facial puffiness (66.5%), vomiting (51.7%) and headache (39.4%) were common symptoms whilst hepatosplenomegaly (61.6%) and generalised lymphadenopathy (60.1%) were common signs. Meningoencephalitis (33.4%) and shock (26.6%) were common complications. Shock, congestive heart failure (CHF), disseminated intravascular coagulation (DIC), haemophagocytic lymphohistiocytosis (HLH) had delayed response to doxycycline therapy.

Conclusions: In this study meningoencephalitis and shock were the common complications of scrub typhus. Meningo-encephalitis, hepatitis and pneumonia had favourable doxycycline response whilst shock, CCF. DIC, HLH and AKI had delayed doxycycline response ($p<0.05$).

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(Key words: Scrub typhus, Eastern India, Trend, Doxycycline response, Complications)

Introduction

Scrub typhus is the commonest rickettsial infection in India leading to multi-organ dysfunction[1,2]. It accounts for about 23% of febrile illness in India[3]. Isolated case reports and case series have been reported from different parts of India[4-6]. However, extensive data on scrub typhus indicating disease trend have not been reported from Eastern India[2,5,6].

Objectives

To study the clinical spectrum and complications of scrub typhus and its doxycycline responsiveness over a period of three years in a tertiary care hospital in Eastern India.

Method

An observational study was conducted in the Paediatric Department of IPGME&R and SSKM Hospital, Kolkata, India, from January 2017 to December 2019. Scrub typhus was suspected in cases having one or more of the following:

- Acute undifferentiated fever of more than 5 days (<5 days if eschar is noted)
- Fever with meningoencephalitis / encephalitis
- Fever with vital organ involvement
- Fever with haemorrhagic manifestations
- Fever with rash / oedema / generalised lymphadenopathy / hepatomegaly / hepatitis with jaundice / dry cough / sepsis of unclear aetiology[6-9].

All patients, aged 12 years or less, clinically suspected of scrub typhus were enrolled in the study. Confirmed scrub typhus was defined as fever >5 days + positive IgM serology (TM IgM ELISA system InBiOS International, Inc.Seattle USA) ± positive Weil-Felix reaction (OX K 1/80 or >)[10,11]. Defervescence within 48 hours was considered additional confirmatory evidence[8,12-14]. Demographic characteristics and clinical features were recorded in a pre-structured proforma. Doxycycline 4.5mg/kg/day in 2 divided doses was given for 7-14 days in laboratory confirmed cases[7]. Time to achieve defervescence and complications were noted. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, renal function tests, serum albumin,

serum electrolytes and chest x-ray were done in all cases at admission and repeated as required. Electrocardiogram and echocardiography were done in cases with congestive cardiac failure. Serum ferritin and serum triglyceride levels were estimated in haemophagocytic lymphohistiocytosis (HLH) suspected cases. Cerebrospinal fluid (CSF) assay was done in patients with neurological presentation. Differential diagnoses like dengue, malaria, infectious mononucleosis, septicaemia, pneumonia, leptospirosis, typhoid and urinary tract infection were ruled out in appropriate cases.

Ethical Issues: Ethical approval was obtained from the Ethics Committee of the Institute of Postgraduate Medical Education & Research, Kolkata (No: Inst/IEC/2018/031). Written informed consent was obtained from the parents and assent, if the child was more than 7 years of age.

Statistical analysis: Categorical variables were expressed as frequency and percentages whilst continuous variables were expressed as mean and standard deviation. Comparison of groups was done using ANOVA, Student t-test and Chi-square test. $p < 0.05$ was considered significant. SPSS version 20 was used for the statistical analysis.

Results

Of 305 patients presenting with fever and features suggestive of scrub typhus, 203 (66.6%) were confirmed as scrub typhus. Mean age of the cohort was 6.3 years with a minimum age of 4 months and a maximum age of 12 years. We had 56.2% males and 43.8% females. One hundred (54%) children were from rural and 85 (46%) from urban areas. Most (85%) cases occurred from July to November. Duration of fever ranged from 3 to 18 days with a mean duration of 9.2 days. Three patients had multiple eschars. Common sites were perineal region (45%) followed by axilla (15%). Eschar was associated with regional lymphadenopathy in 80 (90%) cases. Table 1 shows the clinical and laboratory parameters at presentation and complications over 3 years. Figure 1 is a bar diagram showing clinical features over the 3 years. Figure 2 is a bar diagram showing complications over the 3 years.

Table 1: ***Trend of clinical and laboratory parameters at presentation and complications over 3 years***

Parameter	2017 (n=61)	2018 (n=60)	2019 (n=82)	Total (n=203)
Clinical features				
Mean age of presentation (years)	6.1	6.0	6.7	6.3
Male: female	32:29 (1.1: 1)	35:25 (1.4:1)	47:35 (1.3:1)	114:89 (1.3:1)
Fever>7 days - n (%)	47 (77.0)	45 (75.0)	72 (87.8)	164 (80.7)
Headache - n (%)	28 (45.9)	20 (33.3)	32 (39.0)	80 (39.4)
Myalgia - n (%)	15 (24.6)	15 (25.0)	29 (35.3)	59 (29.0)
Facial puffiness - n (%)	41 (67.2)	40 (66.6)	54 (65.8)	135 (66.5)
Seizures - n (%)	07 (11.5)	10 (16.7)	19 (23.2)	36 (17.7)
Cough - n (%)	24 (39.3)	20 (33.3)	28 (34.1)	72 (35.5)
Pain in abdomen - n (%)	33 (54.1)	22 (36.7)	23 (28.0)	78 (38.4)
Vomiting - n (%)	39 (63.9)	25 (41.7)	41 (50.0)	105 (51.7)
Eschar - n (%)	30 (49.2)	26 (43.3)	33 (40.2)	89 (43.8)
Pedal oedema - n (%)	32 (52.5)	35 (38.3)	45 (54.8)	112 (55.2)
Rash - n (%)	12 (19.7)	05 (08.3)	16 (19.5)	33 (16.2)
Meningeal signs - n (%)	19 (31.1)	21 (35.0)	26 (31.7)	66 (32.5)
Lateral rectus palsy - n (%)	05 (08.2)	03 (05.0)	04 (04.9)	12 (05.9)
Icterus - n (%)	02 (03.3)	05 (08.3)	14 (17.1)	21 (10.3)
Generalised lymphadenopathy - n (%)	36 (59.0)	35 (58.3)	51 (62.1)	122 (60.1)
Hepato-splenomegaly - n (%)	32 (52.5)	40 (66.6)	53 (64.6)	125 (61.6)
Splenomegaly without hepatomegaly - n (%)	01 (01.6)	06 (10.0)	10 (12.2)	17 (08.3)
Laboratory parameters				
Anaemia for age - n (%)	51 (83.6)	50 (83.3)	66 (80.4)	167 (82.2)
Thrombocytopenia - n (%)	36 (59.0)	25 (41.7)	51 (62.2)	112 (55.1)
Neutrophilic leucocytosis - n (%)	50 (82.0)	35 (58.3)	60 (73.2)	145 (71.4)
Hyponatraemia - n (%)	31 (49.2)	30 (50.0)	50 (60.9)	111 (54.6)
Hypoalbuminaemia - n (%)	34 (55.7)	25 (41.7)	38 (46.3)	97 (47.8)
Raised SGOT - n (%)	17 (27.9)	15 (25.0)	33 (40.2)	63 (31.0)
Raised C-reactive protein - n (%)	60 (98.3)	54 (90.0)	75 (91.4)	189 (93.1)
Complications				
Meningoencephalitis - n (%)	21 (34.4)	20 (33.3)	27 (32.9)	68 (33.4)
Shock - n (%)	17 (27.9)	14 (23.3)	23 (28.0)	54 (26.6)
Disseminated intravascular coagulation - n (%)	04 (06.5)	05 (08.3)	04 (04.8)	13 (06.4)
Haemophagocytic lymphohistiocytosis - n (%)	08 (13.1)	10 (16.6)	03 (03.6)	21 (10.3)
Acute kidney injury - n (%)	03 (04.9)	02 (03.3)	04 (04.8)	09 (04.4)
Hepatitis - n (%)	02 (03.2)	05 (08.3)	10 (12.2)	17 (08.3)
Pneumonia - n (%)	06 (09.8)	12 (20.0)	19 (23.2)	37 (18.2)
Congestive heart failure - n (%)	06 (09.8)	09 (15.0)	20 (24.4)	35 (17.2)

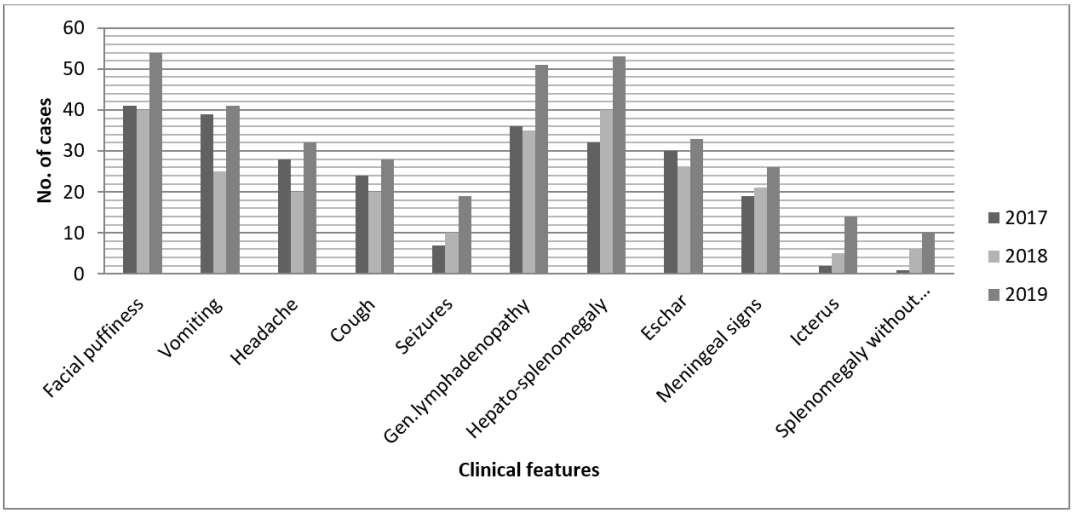

Figure 1: ***Bar diagram showing clinical features over the 3 years***

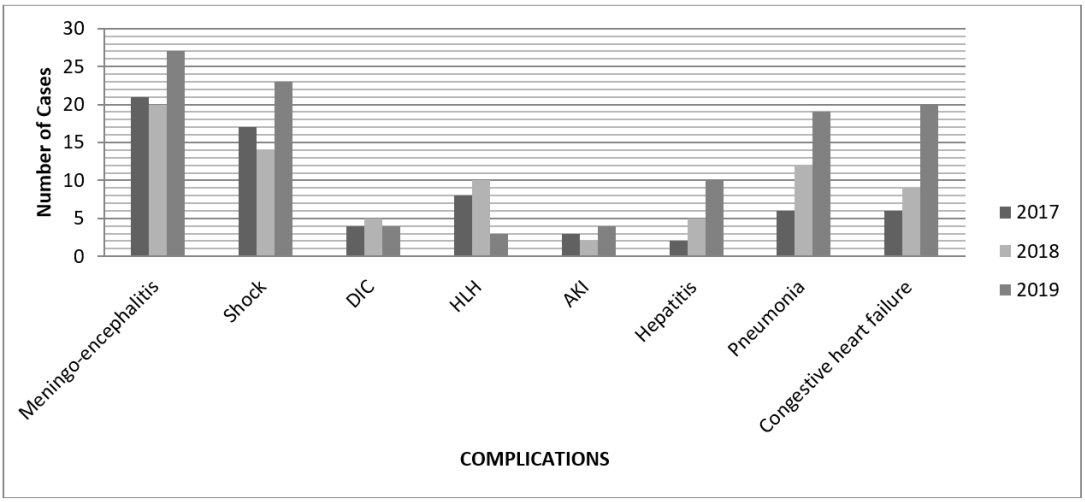

Figure 2: ***Bar diagram showing complications over the 3 years***

Scrub meningoencephalitis was present in 68 cases, 54 of them having lymphocytic pleocytosis and 57 had raised protein in the CSF analysis. Ferritin level was estimated in 31 (15.3%) patients of HLH. Mean value was 6005.8ng/ml, maximum being 31,000ng/ml. Serum triglyceride was raised in 25 patients (mean=350.6mg/dl). Response to doxycycline, assessed by defervescence, was documented in all survivors with mean duration of response 53.4 hours. Among them 155 (77.2%) had a response within 48 hours whereas 46 (22.8%) had delayed response (>48 hours) (Table 2). Neutrophilic leucocytosis, thrombocytopenia, hyponatremia and raised CRP had positive correlation ($p<0.05$) with delayed doxycycline response. Intensive care was required in 37 (18.3%) patients. Inotrope support and mechanical ventilation were required in 32 (15.7%) and 10 (4.9%) cases respectively.

Table 2: ***Doxycycline responsiveness of various complications***

Complication	Doxycycline response *(n=201)*			No response to doxycycline *(n=2)*
	48 hours or < *(n=155)*	> 48 hours *(n=46)*	p-value	
Shock - n (%)	20 (37.0)	34 (63.0)	<0.05	0
CNS involvement - n (%)	55 (80.8)	13 (19.2)	0.464	0
CCF - n (%)	16 (45.7)	19 (54.3)	<0.05	1
HLH - n (%)	13 (61.9)	08 (38.1)	<0.05	1
AKI - n (%)	05 (55.0)	04 (45.0)	<0.05	0
Pneumonia - n (%)	29 (78.4)	08 (21.6)	0.839	0
Hepatitis - n (%)	15 (88.2)	02 (11.8)	0.367	0
DIC - n (%)	05 (38.5)	08 (61.5)	<0.05	0

CNS: central nervous system, CCF: congestive cardiac failure, HLH: haemophagocytic lymphohistiocytosis, AKI: acute kidney injury, DIC: disseminated intravascular coagulation

Only one patient with HLH required definitive management as per standard protocol. Two cases succumbed, one from HLH with multi-organ dysfunction syndrome (MODS) in 2017 and another from congestive cardiac failure (CCF) in 2019. Meningo-encephalitis, hepatitis and pneumonia cases had favourable doxycycline response while other complications were associated with delayed doxycycline response, which was statistically significant ($p<0.05$). Co-infection with infectious mononucleosis and dengue were detected in 5 and 4 patients respectively. All had prompt doxycycline response.

Discussion

Scrub typhus is transmitted to humans by the bites of chigger infected with *Orientia tsutsugamushi*[4,12]. If appropriate treatment is not administered, complications develop by the second week[15]. Immunofluorescence assay, the 'gold standard' to diagnose rickettsial infection, is costly and not freely available[16]. Scrub typhus specific ELISA based IgM assay is the most sensitive test for diagnosis after one week of illness[1].We had male preponderance (1.3:1) in our study similar to study by Bhat NK, *et al*[8]. Rash was found in 16.2% of our patients similar to some studies[8,13]. Higher incidence of rash (23% to 100%) was reported by others[17]. Fever was present in all cases. Most of the cases (80.7%) presented with prolonged fever (>7 days). Facial puffiness (66.5%), vomiting (51.7%) headache (39.4%) and pain in abdomen (38.4%) were common presenting symptoms in our study and the trend was similar in all 3 years, which is comparable to other studies[8,10,17,18].

Common presenting signs were hepatosplenomegaly (61.6%), generalised lymphadenopathy (60.1%) and pedal oedema (55.2%) similar to other studies[1,17,19]. The trend was similar in all 3 years. We found increasing trend of icterus (3.3% in 2017 to 17.1% in 2019) and splenomegaly without hepatomegaly (1.6% in 2017 to 12.2% in 2019) in our study (Table 1). Splenomegaly, found in scrub typhus can help differentiate it from dengue infection. Eschar was present in 43.8% of cases. Multiple eschars, found in several studies[20], were found in 3 of our cases. Careful and thorough physical examination helped in eschar identification and early diagnosis. An eschar, though pathognomonic of chigger bite, is found in 7% -97 % of cases[6,11,21].

Haematological abnormalities on laboratory investigation showed anaemia (82.2%), neutrophilic leucocytosis (71.4%) and thrombocytopenia (55.1%), which is similar to other studies[1,8,14,16]. The haematological abnormalities had similar trends in all 3 years. Meningo-encephalitis (33.4%) with CSF lymphocytic pleocytosis was similar to study by Kumar M, *et al*[19]. Doxycycline responsiveness was studied. Among doxycycline responders (n=201), mean duration of response was 53.4 hours. Though most cases (n=155) responded within 48 hours, patients with HLH, shock, CCF took much more time to respond shifting the mean response time higher. Neutrophilic leucocytosis, thrombocytopenia, raised C-reactive protein (CRP), hyponatraemia showed significant association with delayed doxycycline response.

Incidence of meningo-encephalitis remained almost similar in the 3 years, comprising one-third of cases. Lateral rectus palsy at presentation, though rare, was found in 12 (5.9%) cases in the first week of illness similar to case series[22,23]. The major life threatening complications were shock, HLH, CCF and disseminated intravascular coagulation (DIC). High incidence of shock (26.6%) similar to study by Bhat NK, *et al*[8] was found in our study. We found a similar trend of shock, CCF and DIC in all 3 years. There is an increase in incidence of scrub pneumonia and scrub hepatitis cases over the 3 years (Table 1). One notable trend was a significant reduction in HLH cases (13.1% in 2017 to 3.6% in 2019) over the 3 years ($p<0.05$) most probably due to increased awareness and early institution of doxycycline therapy preventing the progression to HLH. Case mortality rate in our study was 0.98% similar to study by Basu S, *et* al[24]. One case died from complications of HLH and the other from CCF. Both HLH and CCF are two dreaded complications, reported in severe infection[24,25].

We had some rare presentations of scrub typhus in the form of bilateral epididymo-orchitis, acute cholecystitis with cholelithiasis, acute pancreatitis and gangrene of hand, all of which responded to doxycycline therapy. We also had a case of Guillain-Barre syndrome following scrub typhus infection. These are very rare manifestations of scrub typhus[26-29].

Scrub meningo-encephalitis and scrub pneumonia had prompt doxycycline response. However, shock, CCF, DIC, HLH and acute kidney injury (AKI) had delayed doxycycline response which was statistically significant. This delayed response may be due to hypoperfusion leading to poor absorption or due to severity of disease or decreased immunity of the infected host. Similar views have been made by other authors[24,26]. Infection by doxycycline resistant strain or virulent strains of the organism may be another factor for delayed response, though the literature suggests that doxycycline resistance is rare[30].

Conclusions

In this study meningoencephalitis and shock were the common complications of scrub typhus. Meningo-encephalitis, hepatitis and pneumonia cases had favourable doxycycline response whilst shock, CCF. DIC, HLH and AKI had delayed doxycycline response which was statistically significant ($p<0.05$).

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