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Original Article

Pediatric scrub typhus in Southern Kerala: An emerging public health problem

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ABSTRACT

Background: Scrub typhus is a potentially fatal rickettsial infection endemic in Asia. But there are only very few reports of pediatric scrub typhus from Southern Kerala, which is situated in South India.

Objective: To study the clinicoepidemiological profile of pediatric patients with scrub typhus in Southern Kerala.

Methods: Clinical profile of 108 consecutive, 1- to 12-year-old children diagnosed with scrub typhus admitted in a tertiary care teaching hospital in South India from August 2011 to May 2015 was studied.

Results: The median age of affected children was 6.83 years with a male to female ratio 1.42:1. Definite clustering of cases was noted from Nedumangaud Taluk, a hilly area in Trivandrum district (24%). A seasonal pattern was observed with a peak during the months of August–January (84.26%). Most common symptoms apart from fever were cough, abdominal pain, and vomiting. Most common signs were splenomegaly in 68.52% of cases and lymph node enlargement in 59.26% of cases. Eschar was present in 44.44% of cases, with the commonest site being inguinal region. Complications were seen in 9.25% of cases. Myocarditis was the most common complication and one case had associated coronary artery dilatation also. Case fatality rate was only 0.93%. Doxycycline and azithromycin were the antibiotics used. Fever subsided within 24 h of starting treatment in 73.15% of cases and within 48 h in 84.26% of cases.

Conclusion: Scrub typhus is a common cause of fever in South India. Awareness among medical professional should be a high priority as late detection is the cause of failure of treatment, complications, and even mortality.

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1. Introduction

Scrub typhus is a reemerging disease caused by the rickettsial organism *Orientia tsutsugamushi*. It is widely prevalent in various parts of South East Asia. In India too, many isolated outbreaks as well as endemicity have been reported among children.^{1–4} The increasing number of cases from different parts of the country illustrates the magnitude of the burden and urgency to be included in the infectious disease priority list for control, including surveillance.

Portraying the complete clinical picture as well as highlighting the context-specific laboratory features in the subregions of India is important to understand the disease epidemiology. This will also help to explore pattern recognition. This descriptive study is the largest case series study from Southern Kerala among children.

2. Materials and methods

One hundred and eight consecutive 1- to 12-year-old children with scrub typhus attending a tertiary care teaching hospital in Kerala, South India during the period August 2011 to May 2015 were included in the study. This hospital is a referral center with full-fledged pediatric department, including intensive care facilities.

All the cases were diagnosed clinically by the senior pediatricians of the teaching hospital and confirmed by either Scrub Typhus IgM Elisa (in Bios International) or Weil-Felix test (titer >1:160 is used as the cut off). These patients were treated by the senior pediatricians of the institution, which include all the five investigators. Common differential diagnosis like dengue fever, leptospirosis, infectious mononucleosis, and malaria were identified by clinical as well as appropriate laboratory investigations. Coinfected cases of scrub typhus with dengue fever, infectious mononucleosis, and malaria were included in the study. Children who were serologically negative for scrub typhus and infants were excluded from the study population.

Relevant history, clinical features, investigations, treatment, and outcome were recorded in a detailed pro forma by interview, clinical examination, and multiple clinical contacts by the primary investigator. Statistical analysis of the data was performed with Microsoft excel and STATA version X.

Permission was obtained from the ethical committee before conducting the study. Informed consent was obtained from the parents.

3. Results

Among the total inpatients of 42,590 in the hospital, 108 were diagnosed as scrub typhus. During the study period, 106 cases were confirmed as enteric fever, 2046 cases as dengue fever, 25 cases as leptospirosis, and 397 cases as viral hepatitis.

Among the 108 cases analyzed, the median age of affected children was 6.83 years (range 1.5–12 years). 64 cases were of males (59.26%) and 44 were of females (40.74%), with a male to female ratio of 1.42:1. Definite clustering of cases was noted from Nedumangaud Taluk, a hilly area in Trivandrum district

(26 cases – 24.07%). A seasonal pattern was observed. Cases were reported from June to March with a peak during months of August–January (91 cases – 84.26%).

Only one case was referred from the peripheral hospital with the primary diagnosis of scrub typhus. History of mite exposure was reported in only three cases. Diagnosis of scrub typhus was suspected clinically at admission in 24 (22.22%) cases. The differential diagnoses considered were enteric fever in 33 cases followed by infectious mononucleosis and dengue fever in 12 cases each. The average period between time of hospital admission and establishment of diagnosis was 3.2 days. Case fatality was seen in only one patient (0.93%) in whom diagnosis was confirmed after death.

4. Symptom profile

Fever was the presenting symptom in all the patients. Duration of fever ranged from 5 to 28 days. Average duration of fever was 13.35 days. An average of 9.42 days elapsed between onset of fever and hospitalization in the tertiary care hospital (SD 4.17; range 3–21 days) (Fig. 1).

The other presenting features were cough (39.82%), vomiting (38.89%), abdominal pain (34.25%), myalgia (23.15%), headache (24.07%), rash (23.15%), loose stool (10.18%), bleeding manifestation (5.56%), altered sensorium (7.41%), seizures (3.70%), and arthralgia (3.70%).

5. Signs

Most common signs were splenomegaly in 68.52% of cases and lymph node enlargement in 59.26% of cases. Hepatomegaly and eschar were present in 47.22 and 44.44% of cases, respectively. Different combinations of findings of eschar, lymphadenopathy, hepatomegaly, and splenomegaly were observed (Table 1).

Other clinical signs were pallor in five patients, jaundice in one, edema in four, and tachypnea in nine patients.

Fig. 1 – Period between onset of fever and hospitalization. Mean 9.4 days and SD 4.17 (range 3–21 days).

Table 1 – Clinical signs of patients included in the study.

Sign	Total number	Percentage ^a
Splenomegaly	74	68.52
Lymphadenopathy (LNE)	64	59.26
Generalized	43	39.82
Localized	21	19.44
Hepatomegaly	51	47.22
Eschar	48	44.44
Eschar and splenomegaly	34	31.48
Eschar and LNE	30	27.78
Eschar and hepatomegaly	23	21.29
LNE + splenomegaly	46	42.59
LNE + hepatomegaly	30	27.78
LNE + hepatosplenomegaly (HSM)	25	23.15
LNE + eschar + splenomegaly	24	22.22
LNE + eschar + hepatomegaly	15	13.89
LNE + HSM + eschar	14	12.96
HSM alone	9	8.33

^a The total of percentage not adding to 100 because one child has more than one sign.

Commonest site of eschar was in the inguinal region (25%) followed by back and abdomen (16.67% each). The other sites were genitalia (10.42%), chest and axilla (6.25% each), buttocks and umbilicus (4.17% each), and shoulder, hand, arm, popliteal region, and sole (2.08% each) (Figs. 2 and 3).

Fig. 2 – Eschar over the abdomen. **Fig. 3 – Eschar over the scrotum.**

Complications were seen in ten patients (9.25%). Most common complication observed was myocarditis (four cases). One patient with myocarditis died due to refractory shock and acute respiratory distress syndrome and the diagnosis was confirmed after death. Another patient had evidence of coronary vasculitis. Other complications were pulmonary edema in two cases and meningitis, encephalitis, lower motor neuron facial palsy, and pneumonia in one case each. Two children had comorbidities, Down's syndrome, and dilated cardiomyopathy. Three patients needed invasive ventilation.

6. Investigations

Hemogram at initial presentation showed normal total count ($4 \times 10^9/L$ to $11 \times 10^9/L$) at presentation in the majority (64.82%). 34.26% of cases had leucocytosis ($>11 \times 10^9/L$). Only one patient had leucopenia ($\leq 4 \times 10^9/L$). Neutrophilia (neutrophils $\geq 60\%$) was found in 36 cases (33.33%) and lymphocytosis (lymphocytes $>40\%$) was found in 67 cases (62.04%). Reactive lymphocytes were reported in peripheral smear in 72 cases (66.67%). Thrombocytopenia (platelets $<150 \times 10^9/L$) was seen in 53 cases (49.07%). Of the patients with thrombocytopenia, only 11.32% had $<50 \times 10^9/L$. Lowest platelet count was $15 \times 10^9/L$. Hemoglobin was <11 g/dl in 56 patients (66.67%).

Elevated AST (>40 IU/L) was observed in 100 patients (92.59%) and elevated ALT (>40 IU/L) in 80 patients (74.07%). Maximum value of AST was 490 IU/L and ALT was 357 IU/L. Hyponatremia (serum sodium <135 mmol/L) was observed in 87 patients (80.56%). 72 patients (82.76%) had mild hyponatremia with values between 131 mmol/L and 134 mmol/L. Lowest sodium level observed was 116 mmol/L. Four patients had hypokalemia. Hyperbilirubinemia (1.1–3.8) was observed in seven patients (6.48%). 82.81% of cases had elevated erythrocytic sedimentation rate (ESR ≥ 30). Lumbar puncture was done in five cases. Cerebrospinal fluid pleocytosis was observed in one case with 220 cells/mm³ and 60% polymorphs.

Coinfection was observed in 16 cases. Six patients had dengue fever, eight had infectious mononucleosis, one had enteric fever, and one had cerebral malaria.

Doxycycline alone was used for treatment in 78 patients. Dose used was 4 mg/kg/day orally in two divided doses. Azithromycin monotherapy was used in 24 patients and both were combined in 2 cases. Clarithromycin was used as monotherapy in one case. The duration of treatment was 5 days. In three cases, fever resolved without specific treatment and the diagnosis was confirmed after discharge. Fever subsided within 24 h of starting appropriate treatment in 79 patients (73.15%) and within 48 h of starting treatment in 91 cases (84.26%). It took more than 48 h in four patients only.

20 patients had no fever after starting treatment. The average period of defervescence after starting antibiotics was 0.83 days. Resistance to Doxycycline was seen in one case only. That child had fever even after 4 days of treatment and developed myocarditis, congestive cardiac failure, and coronary artery dilatation suggestive of coronary vasculitis. Fever was persisting in spite of Azithromycin, and in view of worsening cardiac status, it was treated with high dose of

Fig. 4 – Duration of hospital stay. Mean 7.7 days (SD 3.4; range 2–21 days).

methyl prednisolone. In one case, fever was persisting even after 4 days of Azithromycin, but subsided within 24 h of replacement with Doxycycline.

Antibiotics were used prior to admission in this hospital in 58 cases (53.7%). The most common antibiotic used was cephalosporin. In our hospital, empirical treatment for enteric fever was given in 37 (34.26%) cases and most common antibiotic used was ceftriaxone followed by ciprofloxacin. Presumptive antimalarial treatment was given in four cases and one case out of this had rapid malarial test positive showing coinfection with malaria.

The mean duration of hospital stay was 7.7 days (SD 3.4; range 2–21 days) (Fig. 4).

7. Discussion

Scrub typhus is documented as an emerging infectious disease among children in Kerala with significant morbidity. The epidemiology revealed a male predominance, mean age of 6.83 years, and a definite seasonal trend with clustering in hilly areas. Most common signs were splenomegaly (68.5%) followed by lymph node enlargement (59.3%), hepatomegaly (47.2%), and eschar (44.44%). The most common site of eschar was inguinal region. A meticulous search for eschar, especially in the inguinal region, back, genitalia, and axilla, is very important in diagnosis due to the nonspecific signs and symptoms. Normal or increased total count, elevated erythrocytic sedimentation rate, elevated liver enzymes, thrombocytopenia, reactive lymphocytes in peripheral smear, and hyponatremia can be considered as early laboratory clues for diagnosing scrub typhus. In spite of a delay in referral, case fatality was low, which may be due to standard management. Myocarditis was the most common complication. One case had associated coronary artery dilatation, which is the first reported case among children. One case of unilateral facial nerve palsy was identified, which is not described in children with scrub typhus till now. Renal involvement was absent in the present series.

The male preponderance (male to female ratio, 1.42:1) was an identical observation with that of Kumar et al.⁴ This may be due to boys more frequently playing outdoors. The mean age at presentation was 6.83 years, which is similar to other studies.⁵ The seasonal trend occurred between August and January (84.26%) when mites are active, that is, during the rainy season. Similar pattern was described from Srilankan and other Indian studies.^{5,6} This is also the optimum season for breeding of rodents. Spatial clustering in hilly area as Nedumangaud (24%) as in the study has been reported from other studies also.⁵

Analysis of referral status indicates a delay in referral, which shows the need for creating awareness among the medical personnel regarding the existence of this disease. Reported history is not dependable regarding exposure to mite because of the small size of mite (<5 mm) and the bite is neither painful nor itchy. This warrants high index of suspicion even in the absence of exposure to mite. Similar experience is reported in a study conducted among Thai children.⁷

7.1. Symptoms

Fever was present in 100% of cases similar to other studies.^{4,5,8,9} Apart from fever, next common symptom was cough (39.82%) similar to the other studies, followed by vomiting (38.89%) and abdominal pain (34.25%), similar to the study from South India.^{4,5} Myalgia was reported in 23.15% of cases, which is similar to the other two Indian studies.^{4,5} Headache was seen in 24% of cases comparable to the study from North-east India.⁵

7.2. Signs

Most common sign reported was splenomegaly (68.52%) followed by lymph node enlargement (59.26%) and hepatomegaly (47.22%). Incidence of splenomegaly was comparable with other studies^{4,10} whereas hepatomegaly was less compared to other studies.^{4,10} Regarding combination of findings, lymph node enlargement with splenomegaly was the commonest (42.59%) followed by eschar with splenomegaly (31.48%). The analysis of clinical examination indicates that the symptoms and signs were nonspecific, which may be one of the causes for delayed referral.

7.3. Eschar

Eschar, which is the most pathognomonic sign, was seen in 44.44% of cases. The reported eschar formation showed substantial variation across different studies. In a study conducted in a tertiary care center in North India,¹⁰ incidence was 13%, and in South India,⁴ it was 11%. In North-east India,⁵ it was 41.7%. In contrast, some studies outside India reported the presence of eschar in 50–80%^{11–13} of cases. The previous exposure to the pathogen in individual populations and variations in cutaneous immunity have been cited as possible explanations for the absence of eschar in scrub typhus.¹⁴ Commonest site in this study was in the inguinal region followed by back, abdomen, and genitalia. The painless eschar is often located in the areas that are least likely to be examined

like inguinal region, back, genitalia, and axilla. Also it is relatively difficult to detect in dark-skinned individuals as in India.

7.4. Investigations

The investigations revealed normal profile of total leucocyte count at presentation in 64.82% of cases, which is similar to other studies in India.^{4,5} In reports from South China, the percentage of cases with increased and decreased WBC count were 32.9% and 27%, respectively whereas in the present study it was 34.26% and 0.92%,¹⁵ respectively. Unlike other studies, the proportion of leucopenia was small in the present study.^{4,5} But our data are correlating with the standard description.¹⁶ Thrombocytopenia in the present study is in 49.07% of cases, which is similar to the study from South China where it was 51.1%. But in Indian studies, varying reports are seen, from 26%⁵ to 100%.¹⁰ Reactive lymphocytosis (66.67% in the present study) can be considered as an important clue for diagnosis.

Elevated liver enzymes with AST > ALT (92.59% and 74.07%) was a finding seen in other studies also.¹⁰ Hyponatremia was observed in 80.56% of cases, which is higher compared to other Indian studies.⁵ This may be an important clue for the early diagnosis of the disease.¹ 82.76% of cases had mild hyponatremia, and so mild hyponatremia also should not be ignored. Abnormal renal function was not seen in any of our patients, whereas it is seen in 20% of cases in Indian studies.^{1,4,10} Elevated erythrocyte sedimentation rate (82.81% in the present study) is another diagnostic clue.¹

7.5. Treatment

Doxycycline is the recommended drug for treating scrub typhus¹⁵ in all age groups. Use of doxycycline in even children less than 8 years of age is safe. Only six or more multiple courses will lead to teeth staining.¹ In our study population, doxycycline was used in 72.22% of cases followed by azithromycin in 22.22% of cases. Duration of treatment was 5 days for both drugs in our study in contrast to other studies where it is 7, 10, and 11 days, respectively.^{4,5,11} The average time for fever resolution after starting treatment was 0.83 days in contrast to 2.4 days in the study from North-east⁵ and 2.8 days reported by Huang et al.¹¹ In our case, doxycycline resistance was noted in only one patient. That child had fever even after 4 days of treatment and developed myocarditis, congestive cardiac failure and coronary artery dilatation suggestive of coronary vasculitis.

Analysis of therapy shows the adherence to standard protocol for treatment, monotherapy with doxycycline in the majority of cases, and relatively short time to fever resolution, considerably reducing hospital stay.

7.6. Complications

Complications were seen in 9.25% of cases only. Even though the major complication observed was myocarditis, it was seen in only 3.7% of the total number of patients in contrast to previous studies in India, which reported 34%.⁴ This may be because even though our institution is a tertiary care center,

more patients are referred to our hospital due to the lack of facilities in the peripheral hospitals. Another reason may be the early institution of appropriate antibiotic treatment in view of the increased awareness among pediatricians in our institution. The random use of doxycycline and azithromycin in peripheral hospitals for respiratory infections may be the third reason for decreased complication rate. One patient died in our study whose diagnosis was confirmed after death, which highlights the importance of high index of suspicion, early diagnosis, and appropriate treatment.

Cranial nerve involvement, including that of seventh nerve, has been reported in literature among adults¹⁶ but not in children. In our series, one patient had unilateral lower motor neuron facial palsy.

In this study, one peculiar complication of coronary artery dilatation suggestive of coronary vasculitis was observed, which is not described in children till now. The patient was a 12-year-old girl who presented with prolonged fever, myalgia, erythematous discrete rashes, painful subcutaneous nodules, generalized lymphadenopathy, and hepatomegaly. This child was both IgM antibody and Weil-Felix test positive. After 72 h of starting doxycycline, there was worsening with development of cardiac failure and new skin rashes. On evaluation, there was borderline coronary artery dilatation of mid left anterior descending branch (4.6 mm) with lack of tapering and mild left ventricular dilatation with ejection fraction of 50% suggestive of coronary vasculitis and myocarditis. Considering doxycycline-resistant scrub typhus, doxycycline was changed to azithromycin. As fever and systemic features were persisting even after 24 h of azithromycin and in view of coronary involvement, methyl prednisolone was pulsed (30 mg/kg/day) for 5 days, suspecting vasculitis. There was dramatic improvement within 12 h. One case of scrub typhus presenting with myocardial infarction was reported in an adult¹⁷ but no cases of coronary involvement are reported in children till now.

The major limitation of the study is that diagnosis was confirmed by either Scrub Typhus IgM Elisa or Weil-Felix test instead of immunofluorescence assay, which is the gold standard test for diagnosis. Immunofluorescence assay is not available in our center.

8. Conclusion

High index of suspicion is important for diagnosing scrub typhus due to the nonspecific nature of clinical features. Prompt treatment causes defervescence within 24 h in majority of cases. Late detection is the cause of failure of treatment, complications, and even mortality. So awareness among medical professionals should be a high priority.

Author contributions

Dr Rekha Krishnan (RK) collected the data. Dr Rajamohanam (RM) helped in analysis and paper writing. Both Dr RK and RM designed the study. Other authors helped to develop the conclusions and discussion part. RK and RM answered to the comments by reviewers and modified the final draft. All authors were involved in the management of the patients.

Conflicts of interest

The authors have none to declare.

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