

ORIGINAL ARTICLE

SCRUB TYPUS IN CHILDREN: CLINICAL PROFILE AND COMPLICATIONS

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Aim: To describe the clinical and laboratory manifestations of scrub typhus in children.

Materials and Methods: One hundred eighty three children with undiagnosed febrile illness from September 2014 to December 2014 were included in the study. All patients were tested for scrub typhus using a commercial Elisa kit for specific IgM antibodies against *Orientia tsutsugamushi*.

Results: Fifty two (28.4%) patients had positive IgM antibodies against *O. tsutsugamushi*. Common clinical feature were fever in 52 (100%), hepatomegaly in 34 (65.3%), nausea /vomiting in 23 (44.2%), lymphadenopathy in 22 (42.3%), abdominal pain and splenomegaly each in 21 (40.3%), generalized swelling in 17 (32%) and headache in 12 (23%) patients. Eschar was seen in one patient only. Among the laboratory parameters 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. Common complication were hepatitis in 49 (94.2%), multi-organ dysfunction syndrome (MODS) in 12 (23.1%), acute respiratory distress syndrome (ARDS) and hypotension each in 10 (19.2%), meningoencephalitis in 5 (9.6%), acute kidney injury in 3 (5.8%), Hemophagocytic lymphohistiocytosis (HLH) and myocarditis in 1 (1.9%) patient each. Five patients died.

Conclusion: Scrub typhus should be considered in the differential diagnosis of acute febrile illness associated with gastrointestinal symptoms, hepatosplenomegaly and lymphadenopathy including those with organ dysfunctions such as hepatitis, thrombocytopenia, MODS, meningitis or ARDS. Empirical treatment for scrub typhus may be given in cases with strong clinical suspicion.

Keywords: eschar, orientia tsutsugamushi, Hemophagocytic lymphohistiocytosis

Introduction

Scrub typhus is a rickettsial disease caused by the organism *Orientia tsutsugamushi*. The organism is transmitted through the bite of larval forms (chiggers) of trombiculid mites. (1) It presents as either a non-specific febrile illness with constitutional symptoms such as vomiting, rash, myalgia and headache or with organ dysfunctions involving organs such as kidney [acute kidney injury (AKI)], liver (hepatitis), lungs [acute respiratory distress syndrome (ARDS)], central nervous system (meningitis) or with circulatory collapse with hemorrhagic features. (1,2) Scrub typhus is one of the differential diagnoses (in addition to leptospirosis, malaria and dengue fever) in patients with hemorrhagic fever especially if associated with jaundice and/or renal failure. (2) Scrub typhus is widespread in the so called "tsutsugamushi triangle" which includes Japan, Taiwan, China and South Korea on the north, India and Nepal on the west and Australia and Indonesia on the south. (3) In India, epidemics of scrub typhus

have been reported from north, east and south India. (4-11) Scrub typhus is grossly under-diagnosed in India due to its non-specific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of diagnostic facilities. After ruling out complicated malaria, and dengue fever, many of these cases remained undiagnosed. The present study was undertaken to assess the etiological agent in these fever cases.

Methods & Materials

This study was conducted in Sir Padampat Mother and Child Health Institute, Sawai Man Singh medical college, Jaipur from September 2014 to December 2014. All consecutive pediatric patients presenting with febrile illness were evaluated. Other causes of fever such as malaria, dengue fever, viral pharyngitis, enteric fever, urinary tract infection were ruled out by history, clinical examination and appropriate laboratory investigations such as urine analysis, complete blood count, platelet count, smear for malarial parasite, rapid antigen test for malaria, and dengue Elisa, widal test and blood culture. Patients were subjected to further investigations such as bleeding and clotting time, prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrin degradation products (FDP), chest X-ray, abdominal ultrasonography, cerebrospinal fluid (CSF) examination, serum ferritin, and triglyceride estimation, renal function tests and liver function tests wherever necessary.

Testing for specific IgM antibodies against *O. tsutsugamushi* was done by Elisa. The study protocol was approved by institutional ethics committee and informed consent was obtained from the parents of children. Patients with positive IgM antibodies against *O. tsutsugamushi* were diagnosed as having scrub typhus. Various complications such as AKI, hepatitis, ARDS, disseminated intravascular coagulation (DIC), meningitis, myocarditis, Hemophagocytic lymphohistiocytosis (HLH) were noted. AKI was diagnosed if there was an abrupt (within 48 hour) reduction of kidney function, defined as an absolute increase in serum creatinine of either >0.3mg/dl or percentage increase of >50% or reduction in urine output (documented urine output of <0.5 ml/kg/hr) in 48 hours. Patients who had elevation of serum bilirubin > 1 mg% and/or elevation of serum transaminases more than the upper limit of normal were labelled as having deranged liver function test. Acute onset of non-cardiogenic pulmonary edema manifesting with bilateral alveolar or interstitial infiltrates on chest radiograph and PaO₂/FIO₂ <300 mm Hg on arterial blood gas analysis confirmed the presence of ARDS. DIC was defined as clinical manifestations of bleeding along with thrombocytopenia and elevated coagulation profile (raised FDP, prolonged PT/INR and aPTT). Myocarditis was defined as presence of systolic global left ventricular wall motion abnormalities on echocardiography along with electrocardiogram (ECG) changes and clinical

findings consistent with left ventricular dysfunction in a previously normal individual. Despite administration of isotonic intravenous fluid bolus > 60ml/kg in 1 hour; decrease in blood pressure (BP) <5th percentile for age or systolic BP < 2 standard deviation (SD) below normal for age or requiring vasoactive drug to maintain BP was labelled as shock. Multi-organ dysfunction syndrome (MODS) was defined by presence of altered organ dysfunction such that homeostasis cannot be maintained without medical intervention. (12) Meningitis was defined as presence of altered sensorium and signs of meningeal irritation associated with elevated proteins and cells on cerebrospinal fluid (CSF) analysis. In laboratory parameters, leukocytosis was considered when white cell count (WBC) was more than 12000 cells/cumm and leucopenia was defined as WBC < 4000 cells/cumm. (13) Thrombocytopenia was considered when platelet count was <150,000 cells/cumm, raised SGOT was > 40IU/L, raised SGPT was > 55IU/L, raised serum creatinine was >1 mg/dl, raised INR was >1.2, raised PT > 14 second and raised bilirubin was >1mg/dl. (14)

The patients, who were serologically diagnosed of having scrub typhus or those with strong clinical suspicion of scrub typhus, were given doxycycline (in children >8years of age, in critically ill patient and those who did not respond to azithromycin) or azithromycin (in children < 8 years of age). All other supportive measures such as hemodialysis, ventilator support, transfusion of blood components, inotropic support were given as per the indications.

Clinical and laboratory features associated with scrub typhus were analyzed.

Results

A total of 183 consecutive patients with undiagnosed fever were included in the study and 52 (28.4%) had positive IgM antibody against scrub typhus. Mean age of presentation was 9.7 + 3.9 years with age range of 4 months to 16 years. Male: female ratio was 1:1. Forty four (84.6%) cases were from rural area. Thirty seven (71%) cases were seen mainly between September and November months which are post monsoon months. The common clinical features are depicted in table 1 and laboratory abnormalities are depicted in table 2. Hepatitis was seen in 49 (94.2%) patients, MODS in 12 (23.1%), ARDS and hypotension in 10 (19.2%) patients each, meningoencephalitis and DIC in 5 (9.6%) patients each, AKI in 3 (5.76%) and myocarditis and HLH in 1 (1.9%) patient each. Five patients (two from ARDS, one from acute liver failure, one from severe shock, and one from MODS) died in the hospital. Remaining patients recovered within one to three days of starting treatment. Azithromycin was given in 37 (71.2%) patients and out of these 28 (75.7%) patients recovered. In rest of cases we added doxycycline.

Table 1: Clinical features of scrub typhus

Clinical features	No of patients [n=52(%)]
Fever (<7 days)	20 (38.4%)
Fever (7-14 days)	25 (48%)
Fever (14-29 days)	7 (13.4%)
Hepatomegaly	34 (65.3%)
Nausea/ vomiting	23 (44.2%)
Lymphadenopathy	22 (42.3%)
Abdominal pain	21 (40.3%)
Splenomegaly	21 (40.3%)
Serositis	17 (32.6%)
Pedal edema	15 (29%)
Headache	12 (23%)
Shock	10 (19.2%)
Myalgia	10 (19%)
Seizure	9 (17.3%)
Cough	5 (9.6%)
Altered sensorium	5 (9.6%)
Maculopapular Rash	4 (7.6%)
Diarrhea	3 (5.7%)
Jaundice	3 (5.7%)
Bleeding manifestation	2 (3.84%)
Eschar	1 (1.92%)

Table 2: Laboratory abnormalities in scrub typhus

Laboratory parameter	No of patient [n =52(%)]
Raised SGOT	49 (94.2%)
Thrombocytopenia	46 (88.4%)
Raised SGPT	41 (78.8%)
Leukopenia	12 (23%)
Leukocytosis	11 (21.1%)
Raised bilirubin	5 (9.6%)
Raised INR	4 (7.7%)
Raised serum creatinine	3 (5.7%)

Discussion

There have been reports of the outbreaks of scrub typhus from various parts of the country in the recent past with serological evidence of widespread prevalence of spotted fevers and scrub typhus in different states. (4,5,7-11) Thus, there was a strong possibility of presence of scrub disease in Rajasthan also but it had not been documented in pediatric age group as yet. In the present study most of the cases were seen during the months of September to December. Such post monsoon surge is reported earlier also. (5-7,9,11) Further, in the immediate post monsoon period (September to early months of the next year), there is growth of secondary scrub vegetation, which is the habitat for trombiculid mites (mite islands). (15) Children play and are also involved in the harvesting activity in the fields where they are exposed to the bites of larval mites. The disease presents as an acute febrile illness with non-specific signs and symptoms. (1) In our study, the commonest presentations were fever with vomiting and pain in abdomen. These findings assume importance, as there is limited available information on the relationship between scrub typhus and gastrointestinal dysfunction. (16) Unlike the usual viral illnesses, the duration of fever in the majority of cases is usually more than 7 days. A necrotic eschar at the inoculating site of the mite is pathognomonic of scrub typhus (1,3), however, it is rarely seen in south East Asia and Indian subcontinent. (5,7,11) In our series, eschar was seen in only one patient. Lymphadenopathy is common in scrub typhus. (8,17) It can be a differentiating feature from malaria and dengue where patients can also have hepatomegaly and splenomegaly as was seen in our patients with scrub typhus. Another important finding noted was the occurrence of capillary leak. Tsutsugamushi infects vascular endothelium leading to vasculitis and organ dysfunction. (2) Vascular injury to capillary endothelium may be the causative factor for capillary leak. Similar to many other case series most patients had elevation of serum transaminases, even without any other evidence of multi-organ dysfunction as scrub typhus hepatitis causes mild portal inflammation and lobular activities without causing significant interface hepatitis or intralobular hepatocyte death due to focal direct liver damage. Therefore, if patients are found with fever of unknown origin and abnormal liver function, we should take scrub typhus into consideration. Other laboratory findings noted were leukocytosis, thrombocytopenia. Leukocytosis is thought to be associated with severe scrub typhus (18,19), these findings need to be validated in a large sample.

The mainstay of diagnosis in scrub typhus is serology. (20) The gold standard serological tests are immunofluorescence antibody test or indirect immunoperoxidase assay (20) but are out of reach in our country owing to high costs. The cheapest test currently available and used extensively in our country is Weil-Felix test (4,6-8,11) which is highly specific, but lacks sensitivity. (17,21) In the present study,

we used ELISA testing for IgM antibodies against *O. tsutsugamushi* for diagnosis. This test has shown good sensitivity and specificity ~90% for detecting specific antibodies (4,20,22) and has been adequately validated. (5)

Complications in scrub typhus develop after first week of illness (1) and are directly related to the blood load of *O. tsutsugamushi*. (23,24) In the present study, the most common organ dysfunction was hepatitis followed by MODS, ARDS, circulatory collapse, meningoencephalitis and AKI. CSF abnormalities in rickettsia meningitis is similar to that of viral or tuberculous meningitis. (24,25) The features favoring rickettsia meningitis are duration of fever more than five days, CSF pleocytosis of lower magnitude, CSF lymphocytes more than 50% and elevation of SGPT. (26)

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hours, maximum 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hours, maximum 2 gm/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV, maximum 4 g/24 hr). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for ≥ 3 days to avoid relapse. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range, 1-5 days). Highly virulent or potentially doxycycline-resistant *O. tsutsugamushi* strains have emerged in some regions of Thailand. Clinical trials showed that azithromycin may be as effective and that rifampicin is superior to doxycycline in such cases. Likewise, a retrospective analysis in Korean children with scrub typhus showed that roxithromycin was as effective as either doxycycline or chloramphenicol, suggesting a role as an alternative therapy for children or pregnant women. (27) In our study most of the patients were given azithromycin and 75% patients recovered. Rest of them responded to doxycycline.

In our study, mortality rate was 9.6%. This is relatively higher as compared to other studies. (5,7,19) It may be because our hospital is a tertiary health center and patients referred are here in late stages and also in critical condition.

In conclusion, our study showed that scrub typhus should be considered in the differential diagnosis of acute febrile illness associated with gastrointestinal symptoms, hepatosplenomegaly and lymphadenopathy including those with organ dysfunctions such as hepatitis, meningoencephalitis, AKI, coagulopathy or ARDS. Though eschar is pathognomonic of the disease, it may not be commonly seen, and its absence does not rule out scrub typhus. As patients respond to doxycycline or macrolides, empirical treatment with these antibiotics may be given in cases where there is a strong clinical suspicion of scrub typhus.

Funding: None

Conflict of Interest : None

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DOI No. 10.7199/ped.oncall.2015.68
