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Scrub typhus meningitis: An emerging infectious threat

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Abstract:
Background: *Scrub typhus is prevalent in India although definite statistics are not available. Recent reports from several parts of India indicate that there is a resurgence of scrub typhus. There have been only few studies on scrub meningitis, most are case report.*
Methods*: A prospective study done in Sir Padampat Mother and Child Health Institute, SMS Medical College, Jaipur to find cases of scrub typhus from August 2014 to December 2014. Diagnosis was made by a combination of an acute febrile illness with a positive scrub IgM ELISA. Lumbar puncture performed in patients with headache, vomiting, meningeal signs, seizures, or altered sensorium.*
Results: *Forty nine cases of scrub typhus were found, and 7 (~15%) had meningitis. There were 25 males and 24 females. Only one patient had an eschar. Mean CSF cell count, lymphocyte percentage, CSF protein, CSF glucose/blood glucose, CSF ADA were 42 cells/µL, 97%, 81 mg/dL, 0.7 and 5.2 U/mL. Complications including thrombocytopenia, severe anemia, acute kidney injury and respiratory failure are more common in scrub typhus meningitis. There were no mortality from meningitis, all made uneventful recovery.*
Conclusion: *Our finding is contrary to current perception that scrub typhus rarely causes meningitis. Meningitis in scrub typhus is mild with quick and complete recovery. Clinical features and CSF findings can mimic tuberculous meningitis, except for ADA levels. Both are endemic in india, so scrub IgM and CSF ADA levels may be helpful in differentiating these two and in avoiding prolonged empirical ATT in cases of lymphocytic meningitis.*
Keywords:*Meningitis, Scrub typhus, Eschar, Orientia tsutsugamushi*
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I. Introduction:

Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi (rickettsia tsutsugamushi). Scrub typhus is a public health problem in Asia, where about 1 million new cases are identified annually and 1 billion people may be at risk of this disease. During World War II, scrub typhus produced considerable morbidity and mortality among troops deployed in Southeast Asia [1].

In India, the presence of scrub typhus and other rickettsial diseases has been known for several decades. However, there has been a considerable decline in the incidence of scrub typhus in the later decades. Recent reports from several parts of India, including south-west India, indicate that there is a resurgence of scrub typhus [2],[3],[4],[5],[6]. In India, scrub typhus has been reported in at least 16 states (Jammu & Kashmir, Himachal Pradesh, Rajasthan, Haryana, Maharashtra, Karnataka, Andhra Pradesh, Kerala, Tamil Nadu, Pondicherry, West Bengal, Sikkim, Uttaranchal, Assam, Arunachal Pradesh, and Nagaland) [7][8][9]. Scrub typhus is grossly under diagnosed in India due to its nonspecific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of diagnostic facilities.

It is a zoonotic disease transmitted by the larval mites (chiggers). The mite has four life cycle stages: egg, larva, nymph and adult [10]. Horizontal transmission occurs in rodents and humans get accidentally infected following bites of chiggers [11]. Vertical transovarial transmission occurs in mites [11] although one case of transplacental spread has been reported in a pregnant woman who delivered a preterm baby with hepatosplenomegaly, meningitis, and sepsis with scrub IgM positivity [12]. Infection spreads through both hematogenous and lymphatic routes [13]. Target site for multiplication are the endothelial cells of the various systems [14].

The infection manifests clinically as a nonspecific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhea, cough, or breathlessness. Chills and fever occur by the 3–4th day of bite, and rash and lymphadenopathy appear at the end of the first week [15].The pathognomonic clinical sign of scrub typhus is "eschar" which may be inconspicuous as it is often present in areas like groin, gluteal folds, breast folds, and external genitalia and may go unnoticed in dark-skinned people.

Serious complications occur during the second week of illness and comprise of pneumonitis, pleural effusion, myocarditis, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), meningitis and multiorgan dysfunction syndrome (MODS) [16] [17]. Most studies of meningitis in scrub typhus are case reports/series. Silpapojakul et al., in 1991 described nine patients (9/72) presenting with meningitis in the

earliest study of rickettsial meningitis [18]. CSF studies were similar to tuberculous meningitis (TBM) and viral etiologies [18]. Another study from south india Viswanathan et al (2013) described seventeen cases (17/65) of scrub typhus meningitis in which CSF findings mimics tuberculous meningitis except ADA levels [19]. Although literature describing various neurological complications other then meningitis include infarction, [20] cerebellitis, [18] haemorrhages, [21] encephalitis, demyelination, [22] subdural hematoma, [23] typhus nodules [24] and meningitis causing altered sensorium, agitation, motor weakness, seizures, neck stiffness, cranial nerve deficits [25].

II. **Material and methods:**

This study was done at the Sir Padampat Mother and Child Health Institute, Jaipur the tertiary care referral hospital of Rajasthan. The study was approved by the Institute Ethics Committee of the SMS Medical College & Hospital, Jaipur. After obtaining written informed consent all children (Birth to 18 years) admitted from August 2014 to December 2014 with unexplained fever were tested for scrub IgM ELISA. Other causes of fever such as malaria, dengue fever, viral pharyngitis, enteric fever, urinary tract infection, tuberculosis, and malignancy were ruled out by history, clinical examination and appropriate laboratory investigations. A detailed history, demographic details, clinical course, and complications were recorded for all children. All routine haematological and biochemistry profiles were noted at admission and follow up.

Meningitis was defined as presence of fever with signs of meningeal irritation and/or altered sensorium and/or seizures, associated with elevated proteins and >5 cells on CSF analysis. 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 [26]. Acute kidney injury 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) [27]. Patients who had elevation of serum bilirubin > 1.2 mg% and/or elevation of serum transaminases more than the upper limit of normal were labelled as having deranged liver function test. Myocarditis was defined as presence of systolic global left ventricular wall motion abnormalities on echocardiography along with 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 below normal for age or require vasoactive drug to maintain BP was labelled as shock. Multi-organ dysfunction was defined by presence of altered organ dysfunction such that homeostasis cannot be maintained without medical intervention. HLH was defined according to current 2008 diagnostic criteria [28]. Severe anemia as hemoglobin <7 g/dL and <8 g/dL in children 6-59 months and ≥5 years respectively; leukocytosis as total leukocyte count >11000 cells/mL; leukopenia as total leukocyte count <4000 cells/mL; thrombocytopenia as platelet count < 100000 cells/mL.

Demographic data, history, examination and investigations were stored in an Excel spreadsheet for analysis. Statistical analysis was performed using STATGRAPHICS Centurion for Windows. Numerical data was analysed by descriptive statistics. Independent–samples T test was performed for continuous variables and they were expressed as means ± standard deviation. Chi square test (or Fischer's exact test) was performed for categorical data. Statistical significance was defined as p value, < 0.05.

III. **Results:**

Out of 183 patients with unexplained fever were seen during this period, 49 tested positive for scrub typhus IgM ELISA. Males constituted 25 (51%) children. The mean age was 7.69 ± 4.85 (range 4 months – 16 years) years and the mean duration of fever at presentation was 8.43 ± 3.98 (range 2–20) days. 42 (85.7%) patients were from rural areas.

The demographic, clinical features and laboratory abnormalities in scrub typhus positive patients are given in Table 1. Fever with vomiting, Pain abdomen, edema, hepatomegaly, splenomegaly, lymphadenopathy, meningitis/meningoencephalitis, anaemia and thrombocytopenia, deranged liver function were significantly more common in patients with scrub typhus (Table 1).

Table No. 1: Demographic, clinical profile and complications in scrub typhus

Parameter	No. of patients (n=49) (%)
Demographic	
Urban	7(14.3%)
Rural	42(85.7%)
Male	25(51%)
Female	24(49%)
Age group	
<2years	8(16.3%)

2-5years	9(18.4%)
>5 years	32(65.3%)
Symptoms	
Fever of <7 days	18(36.7%)
Fever of ≥7 days	31(63.3%)
Headache	9(18.3)%
Vomiting	21(42.8%)
Abdominal Pain	19(38.8%)
Myalgia/Arthralgia	8(16.3%)
Diarrhoea	3(5.7%)
Edema	16(32.6)
Cough	5(9.6%)
Altered Sensorium	3(5.7%)
Seizure	7(14.3%)
Sign	
Maculopapular rash	4(7.6%)
Lymphadenopathy	22(42.3)
Evidence of capillary leak	11(22.4%)
Hepatomegaly	32(65.3)
Splenomegaly	20(40.8%)
Bleeding manifestations	2(3.8%)
Icterus	3(5.7%)
Eschar	1(1.9%)
Signs of meningeal irritation	4(8.2%)
Complications	
Deranged liver function	38(77.5%)
Meningitis	7(14.3%)
ARDS	3(5.7%)
AKI	2(3.8%)
Shock	2(3.8%)
Respiratory failure	4(8.2%)
Myocarditis	1(1.9%)
MODS	4(8.2%)
Pneumonitis	4(8.2%)
Severe anemia	6(12.2%)
Leukocytosis	14(28.6%)
Leukopenia	7(14.3%)
Thrombocytopenia	19(38.8%)
Outcome	
Expired	2(4.08%)

AKI: Acute kidney injury, ARDS: acute respiratory distress syndrome, MODS: multiorgan dysfunction syndrome

Table 2 lists the clinical manifestations recorded in this study population. Seven (~15%) patients had clinical and laboratory evidence of meningitis and male: female ratio for this group was 4:3. None of them had eschar. The mean duration of fever before admission was 5.4 ± 2.4. In addition to fever the main symptoms were vomiting, seizures and altered sensorium. Hepatomegaly, splenomegaly and Lymphadenopathy were noted in 100%, 86%, and 57% of the patients, respectively. The meningitis group also had a significantly higher percentage of patients with elevated transaminases (100%), thrombocytopenia (100%), severe anemia (42.8%), respiratory failure (42.8%) and acute renal injury (28.6%) in comparison to no meningitis group (Table 3). The mean cerebrospinal fluid (CSF) cell count, lymphocyte percentage, CSF protein, CSF glucose/blood glucose and CSF ADA were 42 cells/µL, 97%, 81 mg/ dL, 0.7 and 5.2 U/mL respectively. All CSF samples were negative for gram stain, aerobic culture and acid fast bacilli. CSF pressure recordings were not performed. Five out of seven patients with meningitis had been treated sucessfully with Azithromycin (10 mg OD) except one additionally required chloramphenicol due to early respiratory failure, and a 10 year old boy was initially started only on chloramphenicol. No one recieved Doxycycline or Rifampicin. All patients had quick and complete recovey. The mean duration of defervescence and duration of hospital stay were 3.7 ± 1.5 and 6.3 ± 2.6 days respectively and it is significantly higher in meningitis group

Table No.2: Comparison of clinical manifestations in the meningitis and no-meningitis groups in the scrub typhus study population (no. of patients: 49)

Parameters	**Meningitis group (n=7)**	**No meningitis group (n=42)**	**P-value**
Demographic			
Urban: Rural	0:7	7:35	0.2
Male: Female	4:3	21:21	0.7

Age group			
<2 years	4	4	**0.0016**
2-5 years	1	8	0.7623
>5 years	2	30	**0.027**
Symptoms			
Fever of ≥7 days	2	29	**0.04**
Headache	2	8	0.56
Vomiting	5	16	0.099
Abdominal Pain	1	18	0.15
Myalgia/ Arthralgia	0	8	0.21
Diarrhoea	0	3	0.46
Swelling	1	15	0.26
Cough	0	5	0.34
Altered sensorium	3	0	**0.000**
Siezures	6	0	**0.000**
Signs			
Rash	1	2	0.33
Lymphadenopathy	4	18	0.48
Evidence of capillary leak	2	9	0.68
Bleeding	1	1	0.14
Eschar	0	1	0.7
Hepatomegaly	7	25	**0.04**
Splenomegaly	6	14	**0.009**
Icterus	0	3	0.47
Signs of meningeal irritation	4	0	**0.000**

Table No.3: Comparison of laboratory parameters, complications and outcome in the meningitis and no-meningitis groups in the scrub typhus study population (no. of patients: 49)

Parameters	**Meningitis group (n=7)**	**No Meningitis group (n=42)**	**P-value**
Complications (n)			
ARDS	1	2	0.33
AKI	2	0	**0.0004**
Shock	0	2	0.6
Respiratory failure	3	1	**0.0003**
Myocarditis	0	1	0.17
HLH	0	1	0.17
Pneumonitis	2	2	0.0332
Severe anemia	3	3	**0.008**
Leukocytosis	3	11	0.37
Leukopenia	1	6	1.00
Thrombocytopenia	7	12	**0.0003**
Deranged liver function	7	31	0.1
Investigations			
Hb (gm/dl)	8.27 ± 2.7	9.94 ± 1.98	0.056
Total leucocyte count (mm^3/dl)	13.7 ± 8.9	10 ± 6	0.163
Platelet counts(mm^3/dl)	31.9 ± 16.8	81.5 ± 54	**0.021**
SGPT (IU)	159 ± 100	181 ± 430	0.890
SGOT (IU)	243 ± 282	156 ± 236	0.388
Serum Urea (mg/dl)	53 ± 31.2	35.7 ± 17.9	**0.032**
Serum Creatinine (mg/dl)	0.74 ± 0.18	0.74 ± 0.22	0.995
Outcome			
Defervescence (Days)	3.7 ±1.5	1.83 ± 1.95	**0.019**
Total duration of hospital stay (Days)	6.3 ± 2.56	4.3 ± 1.47	**0.004**
Expired (n)	0	2	0.6

HLH: heamophagocytic lymphohistocytoses

Table No. 4: Cerebrospinal fluid abnormalities in the scrub typhus study population (no. of patients: 7)

Parameters	Results						
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
CSF* cytology(cells/mm3)	92	10	80	143	80	55	43
Lymphocytes %	98	100	90	98	98	95	100
Protein, mg/dl	121	70	55	111	103	50	58
Glucose, mg/dl	58	48	65	53	62	69	54
ADA, U/mL	5	3.5	7.4	4.8	6	4	5.5

CSF: cerebrospinal fluid, ADA: adenosine deaminase

IV. **Discussion:**

Recently, several reports of scrub typhus from various parts of India have been published [1],[2],[3],[4],[5]. Most cases of scrub typhus were diagnosed during the rainy months of June to November. However, Mathai et al. reported more cases in the cooler months in southern India [2]. This correlated with the months with a higher number of field rats infected with O. tsutsugamushi and the months with more mites attached to rodents.

O. tsutsugamushi is an obligate intracellular parasite of phagocytes that invades the central nervous system as part of systemic infection and is found in endothelial cells of blood vessels and in circulating phagocytes. Central nervous system (CNS) involvement is a known complication of scrub typhus which ranges from aseptic meningitis to frank meningoencephalitis [29]. The name "typhus" itself, is derived from the Greek work, "typhos," which means "stupor." A recent case series of scrub typhus from Pondicherry reported meningitis as a common CNS complication [30]. Other neurological complications include seizures, delirium, and hearing loss. However, focal CNS damage was rare, and during the encephalitis stage, few complications like cerebellitis, [19] myelitis, [31]and cerebral hemorrhage [22] are reported.

Severe features of central nervous system involvement, such as neck stiffness, neurologic weakness, seizures, delirium, and coma, have been reported. Meningismus or meningitis has been found in 5.7%–13.5% of patients [29]. The rickettsia directly invades the CSF and has been grownfrom CSF [32]. A prospective study ofThai children revealed that scrub typhus was the second mostcommon cause of aseptic meningitis next to Japanese encephalitis[33]. Involvement is generally due to leptomeningeal infiltration[25]. Histiocytes, lymphocytes and plasma cell infiltration of themeninges and perivascular spaces have been described. None ofour patients had had a repeat CSF study due to serologicaldiagnosis and early clinical recovery.

Meningeal signs were seen in 14% of patients with scrub typhus in a study conducted in Assam and Burma way back in 1946 [34]. In our study 57% had meningeal signs. In a study by Pai et al., on 25 patients with CNS involvement, only half of them had CSF lymphocytosis and only a third had elevated protein [35]; O. tsutsugamushi DNA was isolated in six CSF samples. All our patients had CSF lymphocytic pleocytosis and a 57% had elevated protein (>60 mg). TBM remains the closest differential in our setting. India is one among the five countries that have the highest prevalence of TBM [36] with an estimated mortality of 1.5/100,000 population [37]. Staining for acid fast bacilli(AFB) in CSF has low sensitivity [38] and CSF culture for AFB takes up to 8 weeks and are positive only in 50–75% of cases [39],[40]. Hence other markers are necessary.

Fever >7 days, CSF polys <50%, focal deficits, abnormal movements and optic atrophy had predicted the likelihood of TBM in a Lancet study [38]. Specificity and sensitivity were 98.3% and 54.5% if more than 3 variables were present and 98.4% and 43.5% if one or more predictors were present. In another model, disease duration >5 days, CSF Lymphocytosis >70%, age >30 years and cells <1000 may predict TBM with sensitivity and specificity of 84% and 88% respectively [41]. Both models were based on studies in developing countries, but a single model may not predict TBM in all populations. Adenosine deaminase (ADA) >10 increases the post-test probability of TBM [39]. Hence ADA levels may be helpful in differentiating scrub meningitis from tuberculous meningitis but more studies are necessary in that direction. Scrub typhus meningitis can also be differentiated from TBM by the shorter period taken towards normalization [42].

Specific tests for scrub typhus include indirect immunofluorescence test (IFA), immunoperoxidase test (IPT) and complement fixation test (CFT) [36]. IFA is the standard test for diagnosis, but lack of fluorescent microscopes makes it difficult for most hospitals [19]. IgM ELISA, based on the detection of 56 Da antigen [43] is a dot blot test which has high specificity (~90%) and sensitivity (~90%) when compared to IFA and IPT [19]. A four-fold rise in titre is diagnostic, but it could not be performed due to good clinical response to therapy. Pre antibiotic era mortality was >60% [44] and ~30% in a 2006 series from Vellore [45] but with prompt diagnosis

and therapy, the mortality now is very low. There were no deaths arising from scrub typhus meningitis, partly contributed to earlier institution of azithromycin.

All patients with meningitis empirically had received azithromycin 10 mg/kg Q24 hourly except one which initially started chloramphenicol due to strong suspicion. According to literature Doxycycline remains the drug of choice, but we used azithromycin empirically due to most of patients are of younger age group and risk of renal injury more with doxycycline. In a study by Kriangsak Phimda et al the efficacy of azithromycin was not inferior to that of doxycycline for the treatment of both leptospirosis and scrub typhus, with comparable fever clearance times in the two treatment arms. Adverse events occurred more frequently in the doxycycline group than in the azithromycin group 27.6% and 10.6%, respectively [46],[47]. In some instances, progressive neurological damage has occurred despite treatment [48],[49] with doxycycline either due to resistance, immune-mediated injury or due to drug interaction with oral antacids [50]. Doxycycline is bacteriostatic to O. tsutsugamushi and does not cross the blood brain barrier beyond 15–30%. Only one patient required chloramphenicol after 2 days of Azithromycin therapy who had respiratory failure. In Indian scenario presence of lymphocytic CSF in a given patient, with improvement following antituberculous therapy (ATT) may mask the diagnosis of scrub typhus. Recovery in scrub typhus meningitis is brisk with appropriate therapy without any residual weakness.

V. **Limitations:**

This study had some drawbacks. It was conducted in tertiary centre of rajasthan, so there was a referral bias. Additionally azithromycin largely used to treat pharyngitis in children may mask the cases of scrub typhus. Comparison with another group consisting of patients with tuberculous meningitis was not done in our study. Viral encephalitis, especially HSV related was not ruled out.

VI. **Conclusion:**

Clinical features and CSF findings can mimic tuberculous meningitis, except for CSF ADA levels. Both are endemic in india, so scrub IgM and CSF ADA levels may be helpful in differentiating these two, and in avoiding prolonged empirical ATT in cases of lymphocytic meningitis. Rifampicin based ATT masking the diagnosis of scrub typhus and sometimes results in patients continuing long term therapy for TBM. Therefore diagnosis of scrub typhus meningitis should be largely based on a high index of suspicion and empirical treatment with azithromycin or doxycycline or chloramphenicol must be started, delay in treatment can lead to complications and fatal outcome in Scrub typhus.

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