

Comparison of Scrub Typhus With and Without Meningitis

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Abstract

Objective To compare the children admitted with scrub typhus with and without meningitis.

Methods All children admitted with scrub typhus over a 62 mo period were reviewed. Statistical analysis was performed to compare those with and without meningitis for demographic, clinical, investigations and outcome parameters.

Results Four hundred twenty seven children were admitted with scrub typhus and 63 (14.8%) had meningitis. The mean cerebrospinal fluid white blood cell (CSF WBC) count was 71 cells/cu.mm. with mean lymphocyte proportion of 92%. The mean CSF protein was 67 mg/dl and mean CSF glucose, 55 mg/dl. Of those who had meningitis, 24 (38.1%) had seizures, 17 (27%) had altered sensorium and 37 (58.7%) had nuchal rigidity. Finding an eschar, being male, breathing difficulty, and hepatomegaly were significantly more common in those without meningitis. Children with meningitis also had shorter duration of fever at presentation (median [IQR] 7 [3] days vs. 10 [4] days; $p = 0.028$). Headache and vomiting were significantly more common in those with meningitis. Hemoglobin and platelet were significantly lower in those without meningitis. Duration of hospitalization was significantly longer in those with meningitis, whereas acute respiratory distress syndrome (ARDS) was significantly more

common in those without meningitis. There was no neurological deficit in both the groups. There was no mortality in the meningitis group compared to 3.6% mortality in the non-meningitis group ($p = 0.213$).

Conclusions Meningitis occurs in 15% of those with scrub typhus; those with meningitis have good neurological outcome with little mortality; those without meningitis have more complications and poorer outcome.

Keywords Scrub typhus · Meningitis · Children · Cerebrospinal fluid (CSF)

Introduction

Scrub typhus is caused by *Orientia tsutsugamushi*, a gram negative bacterium and is endemic in the so called tsutsugamushi triangle with an estimated 1 billion people at risk and 1 million estimated cases annually [1]. Scrub typhus is being reported increasingly from many parts of India and has a distinct seasonality [2–6]. Clinical manifestations range from a mild febrile illness to a potentially fatal illness with multi-organ dysfunction. In view of the non-specific nature of symptoms, low index of suspicion and lack of availability of appropriate diagnostic tests, there is delay in the diagnosis leading to considerable morbidity and mortality [7]. Finding an eschar is an important clue to the diagnosis of scrub typhus [8].

Neurological complications of scrub typhus are not uncommon. Manifestations such as meningo-encephalitis and meningitis with or without focal neurological signs, cerebellitis, cerebral hemorrhage, cranial nerve palsies, opsoclonus, transient Parkinsonism and myoclonus, brachial plexus neuropathy, Guillain-Barre syndrome, polyneuropathy and acute disseminated encephalomyelitis have been reported [9–15]. Pathological findings in the central nervous system (CNS)

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show focal or diffuse mononuclear cellular infiltration of the leptomeninges, clusters of microglial cells called typhus nodules and brain hemorrhage. Direct invasion of the CNS by *O. tsutsugamushi* has been detected by polymerase chain reaction (PCR) [16]. Cerebrospinal fluid analysis is abnormal with mildly elevated cells which are predominantly lymphocytes, elevated protein and normal sugar [17, 18]. Though there are many reports of scrub typhus meningitis in adults, there are very few reports of scrub typhus meningitis in children. Bacterial meningitis is considered a serious illness with considerable morbidity and mortality. However, there are reports to suggest that scrub typhus meningitis may not have an adverse outcome [17]. In this report, authors compare children who were admitted with scrub typhus with and without meningitis to determine the differences between them in their clinical profile and outcome.

Material and Methods

The authors retrospectively reviewed the records, after Institutional Review Board (IRB) approval, of all children less than 15 y of age admitted under the Department of Pediatrics at the Christian Medical College (CMC), Vellore hospital with scrub typhus between January 2010 and February 2015. The diagnosis of scrub typhus was based on the detection of IgM in serum to *O. tsutsugamushi*-derived recombinant antigen, performed using the InBiosScrub Typhus Detect™ IgM ELISA kit or a positive Weil Felix test with an OX K titre ≥ 80 in any child presenting with fever for more than 5 d. A diagnosis of scrub typhus meningitis was made if any child diagnosed with scrub typhus also had cerebrospinal fluid (CSF) pleocytosis [CSF white blood cell (WBC) count >5 cells/ μ L]. Descriptive statistics were performed for those with and without meningitis for demographic characteristics (age and sex), clinical characteristics (fever, headache, vomiting, rash, loose stool, abdominal pain, cough, breathing difficulty, eschar, bleeding, hepatomegaly, splenomegaly and anthropometry), investigations (hemoglobin, total white cell count, platelet count, alanine aminotransferase), presence of acute respiratory distress syndrome (ARDS), duration of hospitalization, neurological sequelae and mortality. The demographic and clinical characteristics, and outcome measures were compared between children with and without meningitis using χ^2 test and Fisher's exact test for categorical variables and two tailed *t*-test and Mann-Whitney U test for continuous variables; and their strength of association was evaluated by calculating the odds ratios (OR) with 95% confidence intervals (CI) using logistic regression analysis.

Results

There were 427 children admitted during the study period with scrub typhus. Sixty three (14.8%) of them had

meningitis. Diagnosis of scrub typhus was based on a positive scrub typhus IgM test in 31(49.2%) of those with meningitis and 141(39.7%) of those without meningitis. Weil Felix test was positive in 45(71.4%) of those with meningitis and 265(72.8%) of those without meningitis. Thirteen (20.6%) of those with meningitis had both Weil Felix and scrub typhus IgM test positive and 43(11.8%) of those without meningitis had both Weil Felix and scrub typhus IgM test positive. The differences between those with and without meningitis are shown in Table 1. The mean (± 1 SD) for the CSF total WBC count in those with meningitis was 71(± 109) cells/cumm, with predominantly lymphocytes with mean (± 1 SD) being 92(± 8 %). The mean (± 1 SD) for CSF protein was 67(± 43) mg/dl and sugar was 55(± 10) mg/dl in those with scrub typhus meningitis.

Of those who had meningitis, 24(38.1%) had seizures, 17(27%) had altered sensorium and 37(58.7%) had nuchal rigidity. Finding an eschar (OR 0.34, 95% CI 0.19–0.64; $p < 0.001$), being male (OR 0.41, 95% CI 0.24–0.71; $p = 0.003$), breathing difficulty (OR 0.19, 95% CI 0.06–0.62; $p < 0.001$), and hepatomegaly (OR 0.51, 95% CI 0.27–0.99; $p = 0.028$) were more common in those without meningitis. Children with meningitis also had shorter duration of fever at presentation (median [IQR] 7 [3] days vs. 10 [4] days; $p = 0.028$). Headache (OR 8.44, 95% CI 4.38–16.28; $p < 0.001$) and vomiting (OR 4.33, 95% CI 2.44–7.7; $p < 0.001$) were more common in those with meningitis. Hemoglobin (mean [SD] 10.1 [1.4]g% vs. 9.4 [1.8]g%; $p = 0.003$) and platelet count (median [IQR] 97,000 [107000]/cumm vs. 44,000 [84000]/cumm; $p < 0.001$) were lower in those without meningitis. Duration of hospitalization (median [IQR] 5 [3] days vs. 4 [3] days; $p < 0.001$) was longer in those with meningitis, whereas ARDS (OR 0.32, 95% CI 0.11–0.92; $p = 0.014$) was more common in those without meningitis. There was no neurological deficit in both the groups (Table 1).

The children with meningitis were treated with doxycycline alone in 25(39.7%), azithromycin alone in 3(4.8%), chloramphenicol alone in 4(6.3%), doxycycline and azithromycin in 29(46%) and azithromycin and chloramphenicol in 2(3.2%). There was no mortality in the meningitis group compared to 3.6% mortality in the group without meningitis, although this difference was not statistically significant ($p = 0.231$). Of the 13 children who died, 9 of them died with ARDS, multi-organ dysfunction and refractory shock, 2 died of ARDS and myocarditis, 1 died of ARDS, pneumomediastinum and pulmonary hemorrhage and 1 died with encephalitis and increased intracranial tension. The CSF analysis for the child who died with CNS symptoms showed 2 WBCs which were lymphocytes with 58 mg% protein and 72 mg% glucose. Since this child did not meet the inclusion criteria of >5 WBCs for meningitis, this child was not included in the meningitis group.

Table 1 Comparison of demographic, clinical and outcome measures among children with scrub typhus with and without meningitis

	Meningitis (<i>n</i> = 63)	Non-meningitis (<i>n</i> = 364)	Odds ratio (95% CI)	<i>P</i> value
Age in years: Mean (SD)	8.9 (4.1)	6.3 (3.9)	-	<0.001*
Male: <i>n</i> (%)	24 (38.1)	213 (58.5)	0.41 (0.24–0.71)	0.003^
Eschar: <i>n</i> (%)	13 (20.6)	162 (44.5)	0.34 (0.19–0.64)	<0.001^
Duration of fever in days: Median [IQR]	7 [3]	10 [4]	-	0.028#
Headache: <i>n</i> (%)	28 (44.4)	30 (8.2)	8.44 (4.38–16.28)	<0.001^
Vomiting: <i>n</i> (%)	42 (66.7)	109 (29.9)	4.33 (2.44–7.7)	<0.001^
Rash: <i>n</i> (%)	4 (6.4)	28 (7.7)	0.78 (0.26–2.29)	1.000§
Abdominal pain: <i>n</i> (%)	11 (17.5)	79 (21.7)	0.72 (0.36–1.45)	0.446^
Loose stool: <i>n</i> (%)	3 (4.8)	15 (4.1)	1.11 (0.32–3.96)	0.738§
Cough: <i>n</i> (%)	8 (12.7)	81 (22.3)	0.48 (0.22–1.06)	0.085^
Difficult breathing: <i>n</i> (%)	2 (3.2)	74 (20.3)	0.19 (0.06–0.62)	<0.001§
Bleeding: <i>n</i> (%)	0 (0)	2 (0.6)	-	1.000§
Liver palpable: <i>n</i> (%)	48 (76.2)	316 (86.8)	0.51 (0.27–0.99)	0.028^
Spleen palpable: <i>n</i> (%)	27 (42.9)	172 (47.3)	0.88 (0.52–1.49)	0.518^
Stunted: <i>n</i> (%)	20 (35.7)	93 (29.4)	-	0.346^
Wasted: <i>n</i> (%)	19 (52.8)	110 (37.8)	-	0.083^
BMI: <i>n</i> (%)				
Obese/overweight	4 (7.1)	21 (6.7)	-	0.337
Normal	30 (53.6)	201 (63.6)	-	
Thinness/severe thinness	22 (39.3)	94 (29.8)	-	
Hb%: Mean [SD]	10.1 [1.4]	9.4 [1.8]	-	0.003*
WBC TC: Median [IQR]	10100 [6400]	9850 [7500]	-	0.460#
Platelet: Median [IQR]	97000 [107000]	44000 [84000]	-	<0.001#
ALT: Median [IQR]	61 [65]	56 [62]	-	0.098#
Duration of hospitalization in days: Median [IQR]	5 [3]	4 [3]	-	<0.001#
Neurological deficit: <i>n</i> (%)	0 (0)	0 (0)	-	-
ARDS: <i>n</i> (%)	3 (4.8)	61 (16.8)	0.32 (0.11–0.92)	0.014^
Mortality: <i>n</i> (%)	0 (0)	13 (3.6)	-	0.231§

*Two-tailed t-test

^ Chi-square test

Mann-Whitney U test

§ Fisher's exact test

BMI Body mass index; *WBC TC* White blood cell total count; *ALT* Alanine aminotransferase; *ARDS* Acute respiratory distress syndrome

Discussion

In this study, authors present a series of children with scrub typhus and compared those with and without meningitis. They found that those with meningitis presented to the hospital earlier (7 d vs. 10 d of fever) and had no mortality compared to those without meningitis who had a mortality of 3.6% even though this difference was not statistically significant with $p = 0.231$. There were also no neurological deficits in those with meningitis. In the index study, those with meningitis had a milder course of illness with better outcome compared to those without meningitis.

The authors found 14.8% meningitis in the children with scrub typhus in their study compared to 28% in the pediatric study by Bhat et al. [17] and 20% in adults as reported by Viswanathan et al. [19]. Since the children had lumbar punctures done only if they have clinical symptoms or signs to suggest meningitis, it is possible that the proportion of those with meningitis is underestimated. Comparison of the CSF parameters between present study and other studies is shown in Table 2. The CSF total WBC count was elevated with a predominance of lymphocytes. The CSF protein was also mildly elevated and the CSF glucose levels were normal.

Though there are many neurological manifestations of scrub typhus, the authors have concentrated on those children

Table 2 Comparison of CSF analysis reported in the literature with the present study

	Present study	Bhat et al. [17]	Abhilash et al. [18]
Number of patients	63	27	189
Age group	< 15 y	< 18 y	Adults
Mean CSF total WBC Cells/cu.mm(SD)	71(109)	87(95)	80(121)
CSF lymphocytes % (SD)	92(8)	76(15)	88
Mean CSF protein mg/dl (SD)	67(43)	108(52)	106(81)
Mean CSF glucose mg/dl (SD)	55(10)	64(16)	69(90)

CSF Cerebrospinal fluid; WBC White blood cell

presenting with meningitis in the present study. These children with meningitis had a significantly shorter duration of fever at presentation, similar to the study by Bhat et al. Features of meningitis such as headache (44.4%), vomiting (66.7%) and nuchal rigidity (58.7%) were common in those with meningitis in the index study in contrast to the study by Bhat et al. who reported much lower incidence of headache (25.9%) but a similar proportion of vomiting (66.6%) and meningeal signs (66.6%) [17]. Headache (76–91%) has been more commonly reported in adults [18–21]. Seizures (38.1%) and altered sensorium (27%) were less common in those with meningitis in index study compared to the over 50% seizures and altered sensorium reported by Bhat et al. [17].

The presence of eschar, a pathognomonic feature of scrub typhus, was present in 20.6% of present patients with meningitis. This is similar to the 22.2% in those with meningitis reported by Bhat et al. [17]. In literature on adult scrub typhus, finding an eschar has ranged from 17% to 50%, with the largest study finding 27.4% eschars in those with meningitis [18–20, 22]. Eschars were more often found (44%) in those without meningitis in the index study.

In the present study, hemoglobin and platelet counts were significantly lower in those without meningitis. This association was not seen with other studies [17, 19]. This association in present study is probably due to the fact that children in the non-meningitis group were sicker, as evidenced by a significantly longer duration of hospitalization and significantly higher rates of breathing difficulty and ARDS compared to those with meningitis. Thirteen of 364 (3.6%) children without meningitis died, compared to none in the meningitis group. Of the children who died, all but one had ARDS. ARDS is known to be associated with increased mortality in scrub typhus [17, 23]. Better outcomes with rickettsial meningitis have been consistently documented across several studies, [16, 17, 19, 21] although some studies with small numbers have reported high mortality of up to 25% [20, 22].

The biggest limitation of index study is the retrospective nature of the study with its inherent information bias. However, since scrub typhus is a re-emerging disease, the numbers of patients affected are relatively small and it would require considerable time to do a similar prospective analysis. Another limitation is the use of Weil Felix test for the

diagnosis of scrub typhus. At a cut-off of ≥ 80 , the sensitivity for the Weil Felix test is poor at 30%. However, the specificity and positive predictive value at that cut-off is close to 100% [24]. Hence, authors believe that the diagnosis of scrub typhus is true at the cut-off value of ≥ 80 . The authors restricted their analysis to only those with a diagnosis of meningitis based on an abnormal CSF WBC count. It is possible that they would have missed some patients with CNS scrub typhus disease who had a normal CSF WBC count.

In conclusion, meningitis occurs in about 15% of children with scrub typhus. They tend to present earlier to the hospital with symptoms of raised intracranial tension and, probably due to early appropriate treatment, have a good neurological outcome with little mortality. In contrast, children with scrub typhus without meningitis present later to the hospital and are more likely to have complications and a poorer outcome.

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Compliance with Ethical Standards

Conflict of Interest None.

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