

Comparison of Scrub Typhus Meningitis with Acute Bacterial Meningitis and Tuberculous Meningitis

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Objective: To compare scrub typhus meningitis with bacterial and tuberculous meningitis. **Methods:** Children aged <15 years admitted with meningitis were screened and those who fit criteria for diagnosis of scrub typhus meningitis ($n=48$), bacterial meningitis ($n=44$) and tuberculous meningitis ($n=31$) were included for analysis. Clinical features, investigations and outcomes were compared between the three types of meningitis. **Results:** Mean age, duration of fever at presentation, presence of headache and, altered sensorium and presence of hepatomegaly/splenomegaly were statistically significantly different between the groups. Scrub typhus had statistically significant thrombocytopenia, shorter hospital stay and a better neurological and mortality outcome. **Conclusions:** Sub-acute presentation of meningitis in older age group children, and good outcome is associated with scrub typhus when compared to bacterial and tuberculous meningitis.

Keywords: Encephalopathy, Outcome, Presentation, Rickettsial infections.

Meningitis in children is a serious illness with 20% mortality [1] and 20% long term sequelae in childhood bacterial meningitis [2]; and 20% mortality and 54% neurological sequelae in tuberculous meningitis [3]. Scrub typhus meningitis has negligible mortality or sequelae and occurs in about 25% patients with scrub typhus [4,5]. Making a definite diagnosis of scrub typhus can be challenging and requires a high index of suspicion [6,7]. In this retrospective study, we compared the clinical features, investigations and outcome of scrub typhus meningitis (STM) with acute bacterial meningitis (ABM) and tuberculous meningitis (TBM).

METHODS

After Institutional review board approval, We retrospectively reviewed and analyzed the records of all children aged <15 years admitted under the Department of Pediatrics at the Christian Medical College, Vellore hospital with scrub typhus meningitis, bacterial meningitis, and probable/confirmed tuberculous meningitis between January 2010 and December 2014. Scrub typhus meningitis was defined as fever with CSF pleocytosis (CSF WBC count >5 cells/ μ L) and positive IgM using the InBios Scrub Typhus Detect IgM ELISA kit (manufacturer) or a positive Weil Felix test with an OX K titre ≥ 80 in blood. Bacterial meningitis was defined as any child with fever, CSF pleocytosis (CSF WBC count >5 cells/ μ L) and positive CSF or blood culture for bacteria

other than *Mycobacterium tuberculosis*, or positive Latex agglutination test PCR for bacteria in the CSF. Tuberculous meningitis was included if the patients fit the criteria for definite or probable tuberculous meningitis [8]. Clinical features, investigations and outcome were compared between scrub typhus meningitis and bacterial and tuberculous meningitis. Statistical analysis was performed using STATA 13.

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RESULTS

There were 48 STM, 44 ABM and 31 TBM cases during the study period. In those with STM, 23 were positive by Weil Felix test, 15 by Scrub IgM ELISA and 10 were positive by both. Eleven (22.9%) of the patients with STM had eschar. Of those with bacterial meningitis, the causative organisms were *Streptococcus pneumoniae* in 22 (50%), *Hemophilus influenzae* in 11 (25%), nontyphoidal Salmonella in 3 (6.8%), *Enterococcus spp.* and *Neisseria meningitides* in 2 (4.5%) each, and *S. agalactiae*, *S. pyogenes*, *Burkholderia pseudomallei* and *Acinetobacter baumannii* in one each. Definite tuberculous meningitis was diagnosed in 13 (41.9%) and probable tuberculous meningitis in 18 (58.1%).

Comparative data on the demographic, clinical, investigations and outcome parameters is shown in **Table I**. Children with STM were considerably older

(mean 9.12 years) than ABM (mean 3.1 years) or TBM (mean 6.36 years). Most children (83.3%) with STM presented with 4-10 days of fever, while children with ABM presented earlier (50% within 3 days of fever) and children with TBM later (80.7% over 10 days of fever). Splenomegaly was more common with STM, and hepatomegaly with ABM and TBM. Among the blood investigations, thrombocytopenia showed a strong association with scrub typhus.

STM had a significantly shorter hospital stay and better outcome (less death/premature discharge likely to have caused death and neurological deficits). Children with scrub typhus were treated with doxycycline alone in 18 (37.5%), azithromycin alone in 3 (6.3%), chloramphenicol alone in 3 (6.3%), doxycycline and azithromycin in 20 (41.7%), doxycycline and chloramphenicol in 2 (4.2%), azithromycin and chloramphenicol in 1 (2.1%) and doxycycline, azithromycin and chloramphenicol in 1 (2.1%).

DISCUSSION

Important differences in clinical features (age of presentation, duration of fever and presence of liver or spleen enlargement) between the three types (STM, ABM, and TBM) were observed in this study.

The association between older children and scrub typhus meningitis is similar to that reported by Bhat, *et al.* (mean age of 8 years) [5]. Bacterial meningitis and tuberculous meningitis have been reported in much younger children with median ages of 6 months and 32 months, respectively [9,10]. Fever duration of 4-10 days was significantly more likely with STM in this study. Bhat, *et al.*[5] and Varghese, *et al.* [11] reported a mean fever duration of 7.9 days in children and 8.4 days in adults with STM, respectively. Fever and non-specific symptoms are reported to precede CNS manifestations in childhood tuberculosis meningitis by 13-42 days [12] Splenic enlargement in over half of those with STM is consistent with reported literature [5].

TABLE I DEMOGRAPHIC, CLINICAL AND OUTCOME PARAMETERS IN CHILDREN WITH THREE TYPES OF MENINGITIS (N=123)

Parameters	STM (n=48)	ABM (n=44)	STM vs ABM OR (95% CI)	TBM (n=31)	STM vs TBM OR (95% CI)
Mean age (SD), y	9.12 (3.77)	3.1(4.28)	-	6.36(4.78)	-
Fever					
<3 days, n (%)	2 (4.2)	22 (50)		1 (3.2)	
4-10 days, n (%)	40 (83.3)	14 (31.8)	31.4 (6.5,151.11)	5 (16.1)	4 (0.3,52.5)
>10 days, n (%)	6 (12.5)	8 (18.2)	8.2 (1.4,49.6)	25 (80.7)	0.12 (0.009,1.6)
Headache, n (%)	29 (60.4)	8 (18.2)	6.87 (2.63, 17.94)	17 (54.8)	1.26 (0.50,3.13)
Altered Sensorium, n (%)	23 (47.9)	29 (65.9)	0.48 (0.21,1.10)	24 (80.0)	0.23 (0.08, 0.66)
Seizures, n (%)	20 (41.7)	28 (63.6)	0.41 (0.18,0.95)	17 (56.7)	0.55 (0.22,1.37)
Breathing difficulty, n (%)	1 (2.1)	4 (9.1)	0.21(0.02, 1.98)	0	-
Abdominal, pain, n (%)	9 (19.1)	3 (7.0)	3.16 (0.79, 12.55)	1 (3.2)	7.11 (0.85,59.23)
Rash, n (%)	4 (8.3)	1 (2.3)	0.99 (0.42,36.40)	0	-
Hepatomegaly, n (%)	22 (45.8)	37 (84.1)	0.16 (0.06, 0.43)	28 (90.3)	0.091 (0.02,0.33)
Splenomegaly, n (%)	27 (56.3)	6 (13.6)	8.14 (2.90,22.87)	3 (9.7)	12.0 (3.2-44.9)
Platelet count >150,000/ μ L, n (%)	17 (35.4)	34 (77.3)	0.16 (0.06,0.41)	30(96.8)	0.02 (0.002,0.15)
Median (IQR) CSF WBC count	50.0 [25.0;105]	510 [111;1698]	-	80.0 [22.0;160]	-
Mean (SD) CSF Protein, mg%	78.7 (43.3)	235 (308)	-	142 (104)	-
Mean (SD) CSF Glucose, mg%	39.0 (9.69)	23.7 (16.1)	-	25.2 (15.0)	-
Hospitalization, d, mean (SD)	5.81 (2.27)	9.59 (6.51)	-	12.9 (10.8)	-
Duration of ventilation, d, mean (SD)	4.33 (2.08)	8.4 (6.35)	-	5 (1.41)	-
Death/premature discharge likely causing death, n (%)	0	5 (11.4)	-	3 (9.6)	-
Neurological deficits, n (%)	0	4 (4.6)	-	17 (54.8)	-

CSF: cerebrospinal fluid; WBC: white blood cell; STM: Scrub typhus meningitis; ABM: acute bacterial meningitis; TBM: tubercular meningitis.

Among the blood counts, only thrombocytopenia was significantly associated with scrub typhus meningitis, similar to reports in adults [11]. CSF parameters for STM were comparable to previous reports except for CSF glucose that was considerably lower in our study (39 mg/dL vs 64.2 mg/dL) [5]. Children with STM had significantly less hospital stay, and no neurological sequelae or death. Bhat, *et al.* [5] too reported considerably less mortality with STM compared to scrub typhus without meningitis [5]. This is in contrast with the 25% mortality that has been reported in adults with STM [11]. Eschar, a valuable clue to scrub typhus [13] was present in 23% of our patients, which is similar to reported literature [4,5]. Careful examination of the hidden skin folds of the axillae, groin and genitalia is important. [14].

Our study has a number of limitations such as the retrospective nature of the analysis, the convenience sample used, the reliance on serological tests for diagnosis of scrub typhus, and the reliance on blood serology rather than a CSF-based test for diagnosis of STM. However, with good specificity being reported with these tests, over-diagnosis of STM is unlikely.

In conclusion, scrub typhus meningitis is an important cause of acute and sub-acute meningitis. In any child of older arrange group with meningitis with a sub-acute presentation, presence of splenic enlargement and thrombocytopenia should alert the clinician to the possibility of scrub typhus. Finding an eschar is a valuable clue to diagnosis of scrub typhus. Appropriate specific testing for scrub typhus and specific antibiotic therapy results in good prognosis.

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