

Original Articles

## A retrospective analysis of scrub typhus meningitis in children

\*Soumya Roy<sup>1</sup>, Sumit Datta Majumdar<sup>1</sup>, Subroto Chakrabartty<sup>1</sup>

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### Abstract

**Introduction:** Scrub typhus is a re-emerging threat worldwide and meningitis due to it is being increasingly recognised. There are few studies on paediatric patients with scrub typhus meningitis.

**Objective:** To describe the epidemiological, clinical and laboratory profile of children admitted with scrub typhus meningitis to a hospital in eastern India along with treatment outcome.

**Method:** This is a retrospective analysis of the hospital records from September 2015 to January 2017 of all children between 1 month to 12 years of age admitted to the Institute of Child Health, Kolkata, India, with fever, neck rigidity and evidence of both meningitis and scrub typhus. The epidemiological features, clinical signs and symptoms, laboratory findings and treatment outcomes of the children were noted. Chi-square test was used for comparing categorical variables and the student's unpaired t-test for comparing the continuous variables. A p-value of less than 0.05 was considered statistically significant.

**Results:** There were five children with scrub typhus, with a CSF picture of meningitis during the study period. Mean duration of fever before presentation was  $11.6 \pm 1.8$  days. The male: female ratio was 4:1 and the urban: rural ratio 1:4. The mean age was  $78 \pm 37.5$  months. Vomiting, headache, altered sensorium and seizures were the common symptoms. Signs of meningeal irritation, pallor and lymphadenopathy were the common findings on physical examination.

**Conclusion:** Meningitis is an uncommon complication of scrub typhus in children, only 5 cases being recorded from September 2015 to January 2017 at the Institute of Child Health, Kolkata, India.

<sup>1</sup>Institute of Child Health, Kolkata, India

\*Correspondence: dr.roy85@gmail.com

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### Introduction

Scrub typhus is caused by *Orientia tsutsugamushi* and is a serious re-emerging threat as untreated cases may have a 30-35% mortality<sup>1</sup>. Among its various neurological complications, meningitis is the most common<sup>2</sup>. The intracellular rickettsia apparently enter the central nervous system (CNS) via infected monocytes during meningeal inflammation or through the endothelium of the luminal membrane<sup>3</sup>. Although numerous studies have reported occurrence of meningitis in scrub typhus in children, we have found only one paediatric study that has investigated the features of this meningitis<sup>4</sup>.

### Objective

To describe the epidemiological, clinical and laboratory profile of children admitted with scrub typhus meningitis to a hospital in eastern India along with treatment outcome.

### Method

We did a retrospective study of the hospital records of all children admitted to the Institute of Child Health, Kolkata, India, with fever and neck rigidity between September 2015 and January 2017. Children 1 month to 12 years of age with both evidence of meningitis and scrub typhus without any other obvious co-infection were included in the study. Meningitis was defined by the presence of more than 5 cells in the cerebrospinal fluid (CSF). Scrub typhus was defined by both Weil-Felix test (WFT) and IgM ELISA (for scrub typhus) positivity. The epidemiological features, clinical signs and symptoms, laboratory findings and treatment outcomes were noted. The CSF pictures of three children who suffered from tuberculous meningitis (TBM) (proven by clinical features of tuberculosis, positive geneXpert/cartridge based nucleic acid amplification test and positive response to anti-tubercular drugs) were also collected from the hospital records, so as to compare with the CSF picture of scrub typhus meningitis.

WFT and IgM ELISA (for scrub typhus) are routinely done on all children admitted to our

hospital with clinical suspicion of scrub typhus. WFT is considered positive at titres  $\geq 1:80^5$  and IgM ELISA (In Bios International Inc., Seattle) is considered positive at optical density  $>0.5^6$ . Wherever necessary, tests for malaria, dengue, enteric fever, blood culture and urine culture are also done.

Lumbar puncture (LP) for cerebrospinal fluid (CSF) study (provided no contra-indication exists), is done on any child admitted with fever and any one of the following: (a) neck rigidity, (b) repeated convulsions and/or prolonged convulsions in a child with no other obvious cause of seizure, (c) convulsions in a child less than 6 months or more than 5 years of age with no other obvious cause of seizure, (d) definite evidence of raised intracranial pressure of magnetic resonance imaging (MRI) of brain/ ophthalmoscopy, (e) headache and vomiting with clinical suspicion of meningitis. CSF is routinely tested for cytology, glucose, protein, gram stain, ZN Stain, geneXpert/CB-NAAT and bacterial culture but whenever suspected, Indian ink stain, PCR for Herpes and other tests are also done.

Statistical analysis was performed using GraphPad QuickCalcs and ‘Math is Fun’, two online software available freely on the internet<sup>7,8</sup>. Descriptive data were expressed as mean  $\pm$  standard deviation. Chi-square test was used for comparing categorical variables and student’s unpaired t-test test was used for comparing the continuous variables. A p-value of less than 0.05 was considered statistically significant.

**Results**

We found five children with scrub typhus, with a CSF picture of meningitis during the study period. The epidemiological, clinical and laboratory parameters documented in the records are illustrated in Tables 1-3.

**Table 1**  
*Baseline findings of the children with scrub typhus meningitis*

Characteristic	Result
Number of cases (total)	05
Mean duration of fever before presentation (days)	11.6 $\pm$ 1.8
Male : female	4:1
Urban: rural	1:4
Mean age (months)	78 $\pm$ 37.5
Age 2 – 5 years	02
Age >5 years	03

**Table 2**  
*Clinical features of the children with scrub typhus meningitis*

Feature	Number of cases
Headache	03
Vomiting	04
Altered sensorium	03
Seizure	03
Abdominal pain	02
Oedema	01
Pallor	04
Rash	02
Eschar	01
Lymphadenopathy	04
Hepatomegaly	03
Splenomegaly	01
Signs of meningeal irritation	05

**Table 3**  
*Laboratory results and clinical outcome of the children with scrub typhus meningitis*

Feature	Number of cases
Thrombocytopenia	01
Elevated liver transaminases	03
Haemoglobin (g/dl)	9.6 $\pm$ 1.2
Total leukocyte count /cu mm	13,640 $\pm$ 3876
Platelet count /cu mm	193,000 $\pm$ 147000
SGPT IU/dl	69 $\pm$ 41.6
Hospital stay (days)	9.4 $\pm$ 2.3
Mortality	0

WFT showed both OX 2 and OX 19 to be  $<1:20$ . OX K was 1:160 in 3 cases and 1:320 in 2 cases. IgM ELISA was positive at more than 4 times the reference range in all children (mean 2.829  $\pm$  0.579). CSF gram stain, Ziehl-Neelsen stain, GeneXpert /CB-NAAT and culture were negative. Ultrasonography showed hepatosplenomegaly in 3 children.

In the CSF analysis the mean CSF cell count was 51 $\pm$ 30.1/cu mm (range 20 to 105/cu mm), with 100% lymphocytes in four children and 90% lymphocyte in one child. There was moderate elevation of protein (79.8  $\pm$  51.1 mg/dl, range 10.6 to 165 mg/dl) and almost normal glucose (64  $\pm$  9.9 mg/dl, range 49 to 77 mg/dl).

The CSF findings of the three children who suffered from tuberculous meningitis (TBM) were compared with the CSF findings of the 5 children with scrub typhus meningitis. The children with TBM had a mean CSF cell count of 140  $\pm$  64.8 / cu mm, mean lymphocyte percentage 90.7  $\pm$  7.7, mean protein 276.8  $\pm$  97.9 mg/dl and mean glucose 27.7  $\pm$  7.9 mg/dl. The CSF cell count did not show any significance difference between scrub typhus meningitis and TBM (p=0.06, 95% confidence interval -184.45 to 6.45). However CSF protein was significantly higher (p=0.018, 95%

confidence interval -346.227 to -47.773) and CSF glucose was significantly lower ( $p=0.003$ , 95% confidence interval 17.36 to 55.31) in the children with TBM.

In Table 4, the CSF findings in our study are compared with the CSF findings in a few paediatric and adult studies in the literature.

**Table 4: Comparison of literature on CSF parameters of scrub typhus meningitis with that of present study**

	Our study	Meena <i>et al.</i> <sup>4</sup>	Lurshay <i>et al.</i> <sup>14</sup>	Abhilash <i>et al.</i> <sup>3</sup>	Varghese <i>et al.</i> <sup>15</sup>
Age group	Paediatric	Paediatric	Paediatric	Adult	Adult
No. of patients	05	07	44	189	16
Mean cell count /cu mm	51± 30.1	42	-	80 ± 120.7	83.2 ± 83
Mean lymphocyte %	98 ± 4	97	81.1	87.6	83.9 ± 12.5
Mean protein level (mg/dl)	79.8 ± 51.1	81	103	69.4 ± 89.6	106.9 ± 66.7
Mean glucose level (mg/dl)	64 ± 9.9	58.4	-	105.9 ± 80.9	81.3 ± 44.5

Three children were treated with intravenous (IV) doxycycline, one child with IV azithromycin and one child with oral azithromycin. Fever subsided within 24-48 hours in 2 children (the child treated with oral azithromycin and 1 child treated with IV doxycycline) and within 48-72 hours in the remaining 3 children. There were no complications or mortality.

### Discussion

Although scrub typhus is a re-emerging disease, there are already numerous studies in the medical literature regarding its overall presentation in both adult and paediatric age groups. However, the incidence of meningitis due to scrub typhus varies greatly in different studies<sup>4,9-14</sup>. Unfortunately, almost all studies on paediatric scrub typhus have only reported the incidence of meningitis, with only a few studies describing the characteristics of meningitis. There are several studies reporting the details of scrub typhus meningitis in adults<sup>3,15</sup>. One of the largest studies on scrub typhus meningitis has been published by Abhilash *et al* in 2015, which includes 189 patients of age  $41\pm 16.3$  years<sup>3</sup>. To the best of our knowledge, there has been only one systematic study on scrub typhus meningitis in the paediatric age group, from Jaipur, India published in 2015 on only seven children<sup>4</sup>. Extensive search revealed few incomplete descriptions of one or two cases of meningitis described as part of an article on the overall presentations of paediatric scrub typhus<sup>9,16,17</sup>.

In the present study males were more affected, particularly those more than 5 years of age, probably due to their higher outdoor sports activity. The higher incidence in rural background may be due to more rodent and mite vectors in this environment. Headache (60%), vomiting (80%), altered sensorium (60%) and seizure (60%) were present in most of the patients with meningitis. Similar findings have been observed by Meena *et al* in paediatric patients of scrub typhus meningitis<sup>4</sup> and Abhilash *et al* in adults<sup>3</sup>. However, a literature review revealed that the incidence of these neurological findings (headache etc.) are not as high when a general sample of patients with scrub

typhus (both with and without meningitis) was studied<sup>4,9-13</sup>. For example, in a study by Kumar *et al* on thirty-five children diagnosed with scrub typhus (which included two children with meningitis), the occurrence of headache (11%), vomiting (49%), altered sensorium (17%) and seizure (11%) were much lower than that observed in our study population of exclusively meningitis patients<sup>10</sup>. Thus, the presence of these symptoms should raise the suspicion of meningitis in scrub typhus.

The CSF findings in our study are compared with other studies in Table 4. It appears that our observations correlate well with the other studies. The mean cell count is lower in children than in adults. Children showed more lymphocytic predominance in CSF cytology. Protein is only mildly raised and glucose is almost normal in the CSF, mimicking the picture of aseptic meningitis. Confusion with TBM can often be resolved by the presence of a higher amount of protein and lower amount of glucose in the CSF of patients with TBM, as seen in our cases and the CT/MRI picture of the brain may be characteristic in TBM and serve to differentiate between the two. The clinical picture in scrub typhus meningitis may also be confused with partially treated pyogenic meningitis but Varghese *et al* in a study on adult patients observed that the mean duration of fever in pyogenic meningitis was 3.3 days versus a mean duration of fever of 8.4 days in scrub typhus meningitis<sup>15</sup>. In our study the mean duration of fever was  $11.6\pm 1.8$  days in scrub typhus meningitis. The remaining clinical and laboratory parameters are similar to those observed in studies done on the general presentation of children with scrub typhus<sup>4,9-13</sup>. Thus, although signs like rash, eschar and hepatomegaly as well as markers like anaemia, thrombocytopenia and raised liver transaminases can help in suspecting scrub typhus in febrile children, they probably have no role in predicting or diagnosing meningitis.

Both doxycycline and azithromycin are equally efficacious as treatment for scrub typhus meningitis as described in our study. Phimda *et al* showed that in scrub typhus, the median defervescence time was

48 hours (range 16 to 120 hours) with doxycycline and 60 hours (range 12 to 128 hours) with azithromycin<sup>18</sup>. Sirisanthana *et al* used oral doxycycline<sup>16</sup>, Chanta *et al* used chloramphenicol<sup>17</sup> and Meena *et al* used azithromycin as treatment in their patients<sup>4</sup>. The American Academy of Pediatrics committee on infectious diseases has identified doxycycline as the drug of choice in Rickettsial infection in children of any age<sup>19</sup>.

This study will serve to enrich the scant literature on scrub typhus meningitis in the paediatric age group. In the developing countries, where scrub typhus meningitis, tuberculous meningitis and partially treated pyogenic meningitis are very common, confusion is very likely to arise, unless the paediatrician is well-informed about the detailed clinical and laboratory features of scrub typhus meningitis in children.

### Conclusion

Meningitis is an uncommon complication of scrub typhus in children, only 5 cases being recorded from September 2015 to January 2017 at the Institute of Child Health, Kolkata, India.

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