Clinico-laboratory profile of central nervous system infection by scrub typhus at a tertiary care hospital

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ABSTRACT

Background: Scrub typhus is an emerging epidemic in India. Its course can be complicated by involvement of Respiratory system, cardiovascular system, gastrointestinal system and central nervous system. Central nervous system involvement can lead to major morbidity and mortality.

Methods: It is an observational study conducted in the Department of Pediatrics, Patna Medical College and Hospital, Patna from January 2016 to August 2018. All cases of AES who were serologically proven to be due to scrub typhus were clinically examined, signs and symptoms were noted, and complete blood counts were done. Lumbar puncture was done, and CSF was sent for analysis of cells, sugar and protein, IgM for scrub typhus in CSF, gram staining and CSF culture.

Results: Seventy-eight cases were tested positive for scrub typhus. Incidence of scrub typhus among AES cases was 19.4% in the study. Among cases of Scrub typhus, a male predominance and sex ratio was 1.68. Age at presentation ranged from 2 months to 12 years with a mean age of 7.28 years. Most of the cases were seen in the months of September and October with a mini peak in the month of March. Fever and Altered consciousness were present in all the cases. Among laboratory investigations, thrombocytopenia was the most common feature followed by raised Transaminases. CSF Analysis shows mildly increased cell count with lymphocytic predominance and presence of few polymorphs, sugar mildly decreased, and protein mildly raised.

Conclusions: Scrub typhus is an important causative agent of AES in the Eastern parts of India. It should be suspected in cases which present as AES with symptoms of hepatosplenomegaly, thrombocytopenia, and elevated liver enzymes in addition to dengue encephalitis which forms its close differential.

Keywords: Central nervous system infection, CSF, Scrub typhus, Thrombocytopenia

INTRODUCTION

Scrub typhus is an important cause of acute febrile illness in Eastern parts of India. The causative agent is distinct from, but related to, Rickettsia species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of Orientia tsutsugamushi.1,2 Most infections in children are acquired in rural areas. In India, scrub typhus is an emerging cause of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.3,4

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite (Leptotrombidium), which serves as both vector and reservoir. Transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage
takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among cofeeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

Acute encephalitis syndrome (AES) has emerged as a major epidemic in Bihar and is associated with high mortality. Owing to the increasing burden of disease and its associated morbidity and mortality, studies were undertaken to evaluate specific etiology of AES. One of the studies conducted by the Department of Microbiology of Patna Medical College, Patna along with King George’s Medical University, Lucknow, observed that the positivity rates of Scrub typhus IgM or PCR was 25%, followed by IgM positivity for Japanese encephalitis 8.1%, West Nile virus (6.8%), dengue virus (6.1%), chikungunya virus (4.5%).

**METHODS**

The study was conducted in Patna Medical College and Hospital, Patna, Bihar. Case presenting with clinical diagnosis of AES who were serologically proven to be due to Scrub typhus, from January 2016 to August 2018, admitted in Patna Medical College were enrolled in the study.

**Inclusion criteria**

- Serologically proven cases of scrub typhus
- Age between 1-month to 15 years
- Acute onset of fever
- Change in mental status
- Seizures
- Neurologically normal before the onset of fever.

**Exclusion criteria**

- Known case of seizure disorder
- Fever for longer duration
- Febrile convulsion
- Cerebral palsy.

It is an observational study conducted in the Department of Pediatrics, Patna Medical College and Hospital, Patna from January 2016 to August 2018. All cases of AES who were Serologically proven to be due to scrub typhus were clinically examined, signs and symptoms were noted, and complete blood counts were done.

After clinical stabilization and fundoscopy, lumbar puncture was done, and CSF was sent for analysis of cells, sugar and protein. IgM for scrub typhus in CSF, gram staining and CSF culture. Samples were sent, and cerebral malaria and typhoid encephalopathy were ruled out. ADEM was ruled out based on MRI findings.

**RESULTS**

Out of 397 cases admitted with the provisional diagnosis of AES, 78 cases were tested positive for scrub typhus. Incidence of scrub typhus among AES cases was 19.4% in the study.

Among cases of scrub typhus, 49 were males and 29 were females, having a male predominance and sex ratio was 1.68. Age at presentation ranged from 2 months to 12 years with a mean age of 7.28 years ($\pm 2.84$ years).

Figure 1: Seasonal variation of scrub typhus.

**Table 1: Demographic profile of patients.**

<table>
<thead>
<tr>
<th>Demographic character</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>7.28</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>62.8</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>37.1</td>
</tr>
<tr>
<td>Background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>45</td>
<td>57.6</td>
</tr>
<tr>
<td>Urban</td>
<td>33</td>
<td>42.3</td>
</tr>
</tbody>
</table>

Table 1 demonstrates the demographic characters of the patients of AES due to scrub typhus. Mean age of presentation was 7.28 years ($\pm 2.84$ years). 49 cases were males and 29 cases were females having a male to female ratio of 1.68. 45 patients were from rural background and 33 were from urban background. Rural predominance is expected because of close proximity of dense vegetations, ticks and human inhabitation.
vegetations and close contact with domestic animals. Incidence was noted in rural population due to exposure probably due to the higher exposure to chiggers among patients with a male to female ratio of 1.68, which was reported frequency in literature of 22% to 78%. The bacteria multiply at the inoculation site with the formation of a papule that ulcerates and becomes necrotic, evolving into eschar, with regional lymphadenopathy that may progress to generalized lymphadenopathy within a few days. Vasculitis is the basic pathogenic mechanism in scrub typhus. It is responsible for skin rash, microvascular leakage, edema, tissue hypo perfusion and end organ ischemic injury.\(^5\)

The disease is transmitted to humans through the bite of infected chigger, the larval stage of trombiculid mite.\(^6\) The detection of Eschar is a valuable clinical clue in the diagnosis of scrub typhus, Central Nervous System involvement in the form of Acute Encephalitis Syndrome has seldom been highlighted.\(^4\) Relative unawareness of this presentation of Scrub typhus makes the prompt diagnosis difficult, resulting in significant mortality and morbidity.\(^5\)

In this study, authors described the clinico- laboratory profile of scrub typhus causing Acute Encephalitis Syndrome in a Tertiary care hospital in Bihar. The majority of the cases occurred between the months of September and November, which follow the rainy season and coincide with the peak growth of vegetations and mite population. Similar observations have been recorded by other authors.\(^3\) The mean age of presentation was 7.28±2.84. Which is similar to that reported by other authors.\(^9\) There were more male patients than female patients with a male to female ratio of 1.68, which was probably due to the higher exposure to chiggers among boys, who like to play outdoors.\(^10\) Similarly, a higher incidence was noted in rural population due to exposure to vegetations and close contact with domestic animals.

Among the clinical manifestations, fever and altered sensorium, were present in all the cases as they formed the case definition for Acute Encephalitis Syndrome. Convulsion was seen in 79.4% cases. This is slightly more than Eswardass and Eswardass in 2015 which was 66.6%.\(^11\) Signs of meningeal irritation was present in 23.07% of cases which ranges from 20% to 50% in various other studies.\(^12\) Pain abdomen and vomiting was seen in 53.8% and 35.89% respectively. A study from South India has reported the incidence 51% and 34% respectively.\(^13\) Lymphadenopathy was seen in 46.15% of cases which is reported to be from 28% to 57% in various studies.\(^14\) Incidence of hepatosplenomegaly in present study was 61.5% which ranges from 18% to 88%.\(^15\) 28% of the patients had rash with a reported incidence ranging from 23 to 100 % in the above studies.

The presence of Eschar is a valuable clinical clue in the diagnosis of scrub typhus, but its absence does not rule out the disease. Thrombocytopenia was a major laboratory finding observed in present study with a reported frequency in literature of 22% to 78%.\(^16\) Elevated liver transaminases were seen in the study with SGOT elevations more than SGPT.

### DISCUSSION

Scrub typhus is a well-known mite borne disease in the Eastern States of India and is emerging public health problem in India.\(^1\)\(^-\)\(^3\) Although available medical literatures mention many of the complications of scrub typhus, Central Nervous System involvement in the form of Acute Encephalitis Syndrome has seldom been highlighted.\(^4\) Relative unawareness of this presentation of Scrub typhus makes the prompt diagnosis difficult, resulting in significant mortality and morbidity.\(^5\)

The disease is transmitted to humans through the bite of infected chigger, the larval stage of trombiculid mite.\(^6\) The bacteria multiply at the inoculation site with the formation of a papule that ulcerates and becomes necrotic, evolving into eschar, with regional lymphadenopathy that may progress to generalized lymphadenopathy within a few days. Vasculitis is the basic pathogenic mechanism in scrub typhus. It is responsible for skin rash, microvascular leakage, edema, tissue hypo perfusion and end organ ischemic injury.\(^7\)

In this study, authors described the clinico- laboratory profile of scrub typhus causing Acute Encephalitis Syndrome in a Tertiary care hospital in Bihar. The majority of the cases occurred between the months of September and November, which follow the rainy season and coincide with the peak growth of vegetations and mite population. Similar observations have been recorded by other authors.\(^3\) The mean age of presentation was 7.28±2.84. Which is similar to that reported by other authors.\(^9\) There were more male patients than female patients with a male to female ratio of 1.68, which was probably due to the higher exposure to chiggers among boys, who like to play outdoors.\(^10\) Similarly, a higher incidence was noted in rural population due to exposure to vegetations and close contact with domestic animals.

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The presence of Eschar is a valuable clinical clue in the diagnosis of scrub typhus, but its absence does not rule out the disease. Thrombocytopenia was a major laboratory finding observed in present study with a reported frequency in literature of 22% to 78%.\(^16\) Elevated liver transaminases were seen in the study with SGOT elevations more than SGPT.
Table 4: Comparison of CSF analysis of meningitis due to scrub typhus with other studies.

<table>
<thead>
<tr>
<th>Place</th>
<th>Present study</th>
<th>Pai et al17</th>
<th>Boorugu et al18</th>
<th>Kim et al19</th>
<th>Varghese et al20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>Bihar</td>
<td>Korea</td>
<td>South India</td>
<td>South India</td>
<td>South India</td>
</tr>
<tr>
<td>Range</td>
<td>78</td>
<td>25</td>
<td>39</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td><strong>Mean CSF TC (total count)</strong></td>
<td>73±24.43</td>
<td>54±21.8</td>
<td>47.3</td>
<td>96±54.2</td>
<td>83±34.6</td>
</tr>
<tr>
<td>Range</td>
<td>12-148</td>
<td>0-110</td>
<td>2-450</td>
<td>7-387</td>
<td>24-124</td>
</tr>
<tr>
<td><strong>Mean lymphocyte %</strong></td>
<td>82±12.4</td>
<td>74±16.6</td>
<td>85.3</td>
<td>118±46</td>
<td>831±2.5</td>
</tr>
<tr>
<td>Range</td>
<td>72-91%</td>
<td>11-80</td>
<td>30-100</td>
<td>68-100</td>
<td>38-128</td>
</tr>
<tr>
<td><strong>Mean glucose (mg/dl)</strong></td>
<td>76±46.8</td>
<td>54±22.6</td>
<td>67.6</td>
<td>84±42.4</td>
<td>81±44.5</td>
</tr>
<tr>
<td>Range</td>
<td>43-189</td>
<td>47-84</td>
<td>35-209</td>
<td>34-160</td>
<td>36-167</td>
</tr>
<tr>
<td><strong>Mean protein (mg/dl)</strong></td>
<td>94±45.5</td>
<td>74±56.5</td>
<td>90.6</td>
<td>118±46.6</td>
<td>107±66.7</td>
</tr>
<tr>
<td>Range</td>
<td>54-189</td>
<td>10-110</td>
<td>14-360</td>
<td>32-340</td>
<td>28-178</td>
</tr>
</tbody>
</table>

CONCLUSION

Scrub typhus is an important causative agent of AES in the Eastern parts of India. It should be suspected in cases which present as AES with symptoms of hepatosplenomegaly, thrombocytopenia, and elevated liver enzymes in addition to Dengue Encephalitis which forms its close differential. Unless, there is a high index of suspicion to this condition, timely treatment could not be initiated which could lead to high mortality and morbidity among survivors.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Patna Medical College and Hospital, Patna

REFERENCES

1. Frequently asked Questions Scrub Typhus published by World Health Organization WHO Regional Office for South East Asia.
