Liver dysfunction in children with scrub typhus: association with severity of illness and outcome

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Abstract

**Background:** Liver dysfunction is a common finding in children with scrub typhus. Adult literature has found a significant association between the extent of liver dysfunction and severity of illness and outcome. However, very few studies are available on children.

**Objectives:** To study the extent of liver dysfunction in children with scrub typhus and its association with severity of illness and outcome.

**Method:** It was a retrospective descriptive study conducted on children diagnosed with scrub typhus admitted to a tertiary care centre in south India from January 2016 to December 2020. Children from 1 month to 18 years of age were included. Demographic data, clinical details, laboratory parameters, course of illness and outcome data were collected and analysed.

**Results:** Study population included 143 cases of scrub typhus. Mean age of the study population was 8.4 ± 4.4 years with a male: female ratio of 1.2:1. Fever was present in 100%, myalgia in 54.5%, decreased appetite in 54.5%, jaundice in 8.4% and hepatomegaly in 71.3% of children. Abnormal liver function tests were present in 75.5% children. Elevated aspartate transaminase (AST) was seen in 75.5%, elevated alanine transaminase (ALT) in 67.1%, hypoalbuminaemia in 47.5% and severe hypoalbuminaemia (<2.5g/dL) in 29.4%. Complications included meningitis (13.3%), shock (7.6%), meningoencephalitis (2.7%) and acute respiratory distress syndrome (2%). There were 2 (1.3%) deaths. Children with complications had higher AST (p <0.01), ALT (p = 0.018), low serum albumin (p<0.001) and prolonged international normalised ratio (INR) (p =0.003).

**Conclusions:** Abnormal liver function tests were present in 75.5% of children with scrub typhus. Children with complications of scrub typhus had significantly higher median AST levels, ALT levels, low serum albumin levels and prolonged INR compared to children with no complications.

(Key words: Scrub typhus, Transaminases, Hypoalbuminaemia, Liver dysfunction, Hepatitis, Children)

Introduction

Scrub typhus is one of the common causes of undifferentiated febrile illness in tropical regions. The vector for scrub typhus is chiggers or larvae of *Leptotrombidium mites*. The diagnosis is often missed as the signs and symptoms are similar to other tropical infectious diseases especially dengue fever. Mortality rate ranges from 0-30% in untreated cases. Liver dysfunction is a common finding in scrub typhus. Adult literature has found a significant association between elevated liver enzymes and hypoalbuminaemia with the severity of the illness. However, very few studies are available in children.

**Objectives**

To study the spectrum of hepatic involvement in children with scrub typhus and to correlate liver dysfunction with the severity of illness and outcome.

**Method**

This was a retrospective descriptive study conducted at the department of paediatrics of a tertiary referral care centre in South India.

**Inclusion criteria:** Children from 1 month-18 years of age diagnosed with scrub typhus and admitted during the study period of 5 years from January 2016 to December 2020. The diagnosis of scrub typhus was confirmed by IgM ELISA positivity using commercial kit (In Bios International, Inc., Seattle, WA, USA).

**Exclusion criteria:** Children with scrub typhus who were simultaneously positive for other infections (dengue, malaria, enteric fever, hepatitis A and B, leptospirosis, blood culture positivity) and those with pre-existing liver disease which interferes with

Liver function tests (chronic active hepatitis, cirrhosis, hepatitis B, Wilson disease, thalassaemia). We also excluded those who were diagnosed as scrub typhus based only on OX-K titre in Weil Felix test as well as whose liver function test reports were not available.

Baseline demographic, clinical and laboratory information including haemogram and liver function test were documented.

- **Hepatomegaly** was considered as liver enlargement >2 cm below the right costal margin.
- **Prolonged aspartate transaminase** (AST) was defined as AST >2 times the upper limit of normal (40 IU/L).
- **Prolonged alanine transaminase** (ALT) was defined as ALT >2 times the upper limit of normal (40 IU/L).
- **Elevated serum bilirubin**: was defined as total serum bilirubin >2 mg/dl.
- **Hypoalbuminaemia**: was defined as serum albumin levels <3.4g/dL. Severe hypoalbuminaemia was considered if the serum level was <2.5g/dL.
- **Prolonged international normalized ratio** (INR) was defined as INR>1.5.

In the present study, complications of scrub typhus were defined as follows:

- **Hypotension** was defined as a systolic blood pressure below the 5th percentile for the corresponding age, sex and height.
- **Acute respiratory distress syndrome** (ARDS) was defined as per paediatric ARDS criteria.
- **Acute kidney injury** (AKI) was considered as per Kidney Disease Improving Global Outcomes (KDIGO) definition and classification.
- **Myocarditis** was diagnosed when the following conditions were observed: (i) Clinical findings consistent with left ventricular dysfunction (ii) Presence of global left ventricular wall motion abnormality on echocardiography (iii) elevated CPK-MB levels in the blood with or without electrocardiographic abnormalities.
- **Meningoencephalitis** was considered in the presence of altered sensorium along with meningeal signs and/or seizures along with positive cerebrospinal fluid findings.
- **Multiple Organ Dysfunction** (MODS): dysfunction of more than 1 organ requiring intervention to maintain homeostasis.

The extent of hepatic dysfunction was compared between children with complications and those without complications. The length of PICU stay and total duration of hospital stay were recorded. Outcome was defined in terms of mortality and survival.

**Ethical issues**: Approval for the study was obtained from the Institutional Ethics Committee of Kasturba Medical College and Kasturba Hospital (No. IEC: 919/2020) on 08.12.2020. Being a retrospective study informed consent was not a possibility.

**Statistical analysis**: Obtained data were analysed using the Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive data were expressed as frequencies and percentages. Mean and standard deviation were computed for the variables following normal distribution curve, while median and inter-quartile range were computed for non-parametric data. Fisher exact test was used to test categorical variables. Student t-test or Mann Whitney test was used to compare mean or median value of parameter between 2 groups. p-value of <0.05 was considered statistically significant.

**Results**

A total of 188 children with scrub typhus was admitted during the study period. After excluding 45 children, the final study population included 143 children as depicted in Figure 1.
The mean age of the study population was 8.4 ± 4.4 years with a range of 10 months to 18 years. The majority (66.4%) of children were in the age group of 5-10 years. There were 2 infants. Boys were more affected than girls with male-to-female ratio of 1.2:1.

Symptoms and signs of children with scrub typhus are summarised in table 1. The mean duration of illness prior to admission was 5.3±2.58 days with a range of 1-7 days. Hepatomegaly was present in 71.3% children. Maculo-papular rash involving palms and soles was observed in 20.3% children while eschar was present in 12.6% children.

Baseline liver function tests are summarized in table 2. Abnormal liver function tests were present in 75.5% of patients. Elevation of AST and ALT by 3 times the upper normal limit was observed in 47 (32.8%) and 25 cases (17.4%) respectively. Hypoalbuminaemia was present in 68 (47.5%) while severe hypoalbuminaemia (<2.5g/dL) was present in 42 (29.4%) children. Liver function tests normalized within 1 week of hospital stay in 56% of children, while in the remaining children normalization of LFT was documented within the next 4 weeks.

Complications of scrub typhus were observed in 52 (36.4%) children. They included meningitis/meningoencephalitis in 18 (12.6%), shock in 12 (8.4%), pneumonia in 9 (6.3%), ARDS in 4 (2.8%), myocarditis in 4 (2.8%), AKI in 2 (1.4%), MODS in 2 (1.4%) and purpura fulminans in 1 (0.7%).

Thirty-six (25.2%) children required admission to the paediatric intensive care unit (PICU); 12 children required inotropic support and 6 required mechanical ventilation. The mean duration of PICU stay was 4.1±2.04 days (range 1-7 days). The mean duration of hospital stay was 5.2±3.02 days (range 2-12 days).

Doxycycline was used in 95.1% of children. Chloramphenicol was used in 3.6% of children; 2 (1.4%) children were treated with azithromycin.

Mortality was observed in 2 children. Both children developed refractory shock with MODS. Both children had AST and ALT levels of >1000 IU/L, severe hypoalbuminaemia and prolonged INR.

The comparison of LFT parameters with severity of illness (between children with complications and those without complications) is shown in table 3.

Mann-Whitney U test was used to analyse data for AST and ALT levels as the values were not normally distributed. It was found that elevated AST and ALT levels, hypoalbuminaemia and prolonged INR were associated with increased risk of complications and this was statistically significant. Odds ratio for complications were 6.12, 4.18, 10.2 and 13.7 respectively. The average value (mean/median) of LFT parameters were compared between the 2 groups. It was found that children with complications had higher median AST (p<0.01), ALT levels (p=0.018), low serum albumin levels (p<0.001) and prolonged INR (p=0.003). All children with severe hypoalbuminaemia (n=42) were in the complications group. However, the association of mean total serum bilirubin levels with complications was not significant (p = 0.1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With complications (n=52)</th>
<th>Without complications (n=91)</th>
<th>Odds ratio [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated aspartate transaminase (n=108)</td>
<td>48 (135 [85.2, 272.4])</td>
<td>60 (67 [42, 123])</td>
<td>6.12 [1.97, 25.56]</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Median aspartate transaminase (IQR) IU/L</td>
<td>104 (52.2, 118.4)</td>
<td>56 (37.4, 92.6)</td>
<td>4.08 [1.65, 11.21]</td>
<td>0.008*</td>
</tr>
<tr>
<td>Elevated alanine transaminase (n=96)</td>
<td>44 (10.4 [5.2, 118.4])</td>
<td>52 (46.2 [37.4, 92.6])</td>
<td>10.41 [2.08, 12.46]</td>
<td>0.007*</td>
</tr>
<tr>
<td>Median alanine transaminase (IQR) IU/L</td>
<td>10.4 [5.2, 118.4]</td>
<td>5.2 [3.7, 9.2]</td>
<td>2.28±0.74</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Elevated total serum bilirubin (n=12)</td>
<td>10 (0.32, 4.95)</td>
<td>2 (0.44, 1.49)</td>
<td>13.7 [1.68, 63.56]</td>
<td>0.003*</td>
</tr>
<tr>
<td>Median total serum bilirubin (IQR) IU/L</td>
<td>10 (0.32, 4.95)</td>
<td>2 (0.44, 1.49)</td>
<td>13.7 [1.68, 63.56]</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

CI: confidence interval; *Fisher’s exact test; #Mann-Whitney U test; $Student-T test INR: International normalized ratio

The prevalence of hepatomegaly varies in different studies. Studies by Pathak S, et al, in central Nepal and Balaji J, et al, in south India showed hepatomegaly in 47% and 62% respectively. In current study, hepatomegaly was noted in 71.3% of cases. Previous studies have demonstrated that the prevalence of serum aminotransferase elevation ranges from 34% to 96%. In the study by Su TH, et al, serum aminotransferase elevation predicted the diagnosis of scrub typhus, especially in those patients without eschar. The median AST level of children in the present study was 92 [56, 372] IU/L [Q1, Q3] which itself is >2 times the upper limit.

The direct cytotoxic effect versus immune mediated damage in the aetiopathogenesis of liver cell injury has been debated. O. tsutsugamushi has been visualized in infected hepatocytes through electron microscope. It is believed that it’s the triad of host immune reaction, organism load, and virulence plays important role in hepatic dysfunction.

Risk factors reported to be associated with severe illness in scrub typhus include malnutrition, anaemia, dyspnoea at admission, leucocytosis, high C-reactive protein and elevated hepatic transaminases. Very few studies are available in children regarding liver dysfunction and the spectrum of liver involvement in scrub typhus.

Few studies have demonstrated the elevation of total bilirubin as a common marker of hepatocellular dysfunction in scrub typhus. In the present study, serum bilirubin was elevated in only 8.3% of the study population and there was no statistical significance in the difference between mean TSB levels between the 2 groups. In other studies,

... elevated total serum bilirubin ranged from 7.4% to 19.7%.16,17

Hypoalbuminaemia was found to be significantly associated with an increased risk of complications in the present study which was comparable to previous studies19. Children with complications were observed to have low mean serum albumin (2.28±0.74 vs. 3.26±0.61) and this was statistically significant (p<0.001). It was also observed that all children with severe hypoalbuminaemia were present in the complication group. Though we found prolonged INR in 8 children, none of them had significant bleeding manifestations.

Doxycycline is the mainstay of treatment for scrub typhus. Recommended dose is 4-4.5mg/kg/day in 2 divided doses for >40kg body weight for 7-10 days20. In severe cases IV doxycycline can be used. Azithromycin is an effective alternative. In the current study azithromycin was used in 2 children under 2 years of age, where doxycycline is relatively contraindicated.

Conclusions
Abnormal liver function tests were present in 75.5% of children with scrub typhus. Children with complications of scrub typhus had significantly higher median AST levels, ALT levels, low serum albumin levels and prolonged INR compared to children with no complications.

References
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