

PAEDIATRIC SCRUB TYPHUS: CLINICAL PROFILE, LABORATORY DERANGEMENTS AND COMPLICATIONS WITH SPECIAL REFERENCE TO LIVER FUNCTION TEST AS A PREDICTOR OF COMPLICATED PAEDIATRIC SCRUB TYPHUS

B. Guptesh², Swarupa Panda¹, Nibedita Pradhan¹, Subhashree Kar^{1*}

¹.Associate Prof Department of Pediatrics, SVPPGIP and SCB Medical College, Cuttack

². Senior Resident Department of Pediatrics, MKCG Medical College, Berhampur

³. Assistant Prof Department of Pediatrics, SVPPGIP and SCB Medical College, Cuttack

^{4*}. Assistant Prof Department of Pediatrics, SVPPGIP and SCB Medical College, Cuttack

Corresponding Author

Dr. Subhashree Kar,

Assistant Professor

Department of Pediatrics,

SVPPGIP and SCB Medical College, Cuttack

Email: drsubhashreekar@gmail.com

Abstract

Pediatric scrub typhus is a new endemic now a days in our part of world with complicated patients needing admission is quite common. derangement in liver function is very commonly associated with complicated scrub typhus patients along with other parameters. This study depicts deranged liver function as a consistent marker of complicated scrub typhus along with clinical features, lab parameters and complications.

Keywords- scrub typhus, complications, liver function test, pediatrics

Introduction

Scrub typhus is one of the major causes of acute febrile illness in children leading to hospitalization in developing countries like India(1). Many recent reports from different states of India have led to an increased awareness about scrub typhus and its complications(9), but very few studies are done regarding the complications of scrub typhus in children. This study provides an overview of clinical profile, laboratory derangements, various complications and the changes in liver function tests in pediatric scrub typhus and their correlation with complicated scrub typhus infection.

Materials and Methods

Study design-

This study was conducted as a prospective observational study done at S.V.P. Postgraduate Institute of Pediatrics & S.C.B. Medical College and Hospital, Cuttack over a span of 2 years.

Participants-

All hospitalized children aged < 15 years who presented with fever for more than five days were tested for IgM antibody against *O. tsutsugamushi* using ELISA method and those tested positive were included in our study. Patients diagnosed to have infections other than Scrub typhus and those having co-morbid conditions like complicated acute malnutrition, chronic liver disease, chronic kidney disease, known heart disease, were excluded from the study. The demographic profiles and detailed history were taken, clinical examination was conducted and noted in a predefined proforma. All of the patients were treated with intravenous doxycycline initially followed by oral formulation of doxycycline. Liver function test including serum total and direct bilirubin, serum alanine and aspartate transaminases, serum alkaline phosphatase, serum albumin & PT INR were done on the day of admission. Liver dysfunction was defined as presence of any of these- raised serum alanine aminotransferase (ALT) for 1–9 years >55 IU/L and 10–16 years >45 IU/L, raised serum aspartate aminotransferase (AST) > 45IU/L, elevated serum total bilirubin >1 mg/dL, low albumin level <2.5 gm/dl, elevated PT-INR value >1.5.

After obtaining the data all the patients were divided into two groups, depending on the presence or absence of complications. Group A included those children having any one of the pre-defined complications and Group B was constituted by those children having none of the predefined complications. The various clinical features and LFT parameters were compared between these two groups.

Statistical analysis-

The demographic and clinical parameters were recorded and the categorical data were expressed as percentage and continuous data were expressed as mean and standard deviation. The categorical data were compared using Fischer exact test and the continuous data were compared using independent sample T test. The LFT values were expressed as median and interquartile range, and compared between two groups using independent sample T test. Multivariate logistic regression analysis was done to determine the factors independently associated with complication of scrub typhus. All of the statistical tests were performed using SPSS version 26 for windows (IBM Corporation, Armonk, NY, USA).

Results:

A total of 240 children was diagnosed to have scrub typhus with positive IgM ELISA from September 2019 to August 2021. Only 35 (14%) cases were admitted in PICU, and the rest of them were managed in ward. The female to male ratio was 0.79 :1 (106:134). The age of the patients ranged from 2 months to 13 years with mean age of 4.9 years. Children between 3 and 6 years of age accounted for the most of the cases i.e., 28%. The highest number of cases were observed between the months of June and October i.e., 177 (73%)

In our study fever was present in all of the patients. In fact, fever was the only complain of most the patients (45%). The duration of fever prior to admission to the hospital ranged from 2 to 17 days, mean being 9 days. Along with fever, most of the patients presented with complain of vomiting (7.92%), which

was the second most common symptom of pediatric scrub typhus in current study. Among other symptoms nonspecific pain abdomen was present in 19 (14.4%), non-productive cough in 15 (6.25%), convulsions in 13 (5.42%), conjunctival congestion in 9 (3.75%), loose stool in 8 (3.33%), abdominal distention in 7 (2.92%) head-ache in 6 (2.29%) and altered mental status in 3 (1.25%).

On clinical examination of patients, pallor was noted in 72(30%), lymphadenopathy in 121(50.4%), maculopapular rash in 20(8.3%), facial puffiness in 150 (62.5%), pedal edema in 62(25.8%), isolated hepatomegaly in 110 (45%), isolated splenomegaly in 3(1.3%), and hepatosplenomegaly in 77(32.1%). Eschar was found in 162(61%) of cases in our study, and the most common site of eschar was inguinal region (28.57%), followed by trunk (25.71%), and lower limb (22.85%).

Out of 240 patients, 93 (39%) presented with or developed complications during hospital stay, and 147 (61%) patients had no complications. Meningoencephalitis was found to be the most common complication (41.9% of all complicated scrub typhus). Myocarditis with congestive cardiac failure was the 2nd most common complication (38.7% of all complicated scrub). Septic shock was noted in 30% of all complicated scrub typhus, pneumonia in 15%, ARDS in 12%, acute kidney injury in 12%. 9 patients suffered from multiorgan dysfunction syndrome (MODS), and 6 of them developed disseminated intravascular coagulation (DIC). Despite of all available measures 6 patients died of MODS and DIC.

Most of the patients in our study showed some amount of hepatic dysfunction in the form for deranged liver function test. 212 (88%) out of 240 patients showed abnormal LFT. The data showed elevated alanine amino transferase/ALT (mean: 121.9IU/L, Interquartile range: 38 – 136 IU/L), aspartate amino transferase/AST (140.9 IU/L, 48 – 162 IU/L), serum alkaline phosphatase (226.1 IU/L, 123 – 262 IU/L), total bilirubin (0.7mg/dl, 0.2 - 0.63 mg/dl), direct bilirubin (0.4 mg/dl, 0.1 - 0.25 mg/dl), PTINR (1.3, 1 - 1.6), low serum albumin (2.5 g/dl, 1.9 - 3.4 g/dl). Serum bilirubin was elevated in 10% of cases. Serum ALT and AST levels were elevated in 70%,77.9% of cases. Serum alkaline phosphatase levels were high in 45%. Low serum albumin was found in 48.3% of cases and PT INR levels were high in 4.1% of cases.

Up on doing comparison using statistical tests, it was found that there were no significant differences in age and sex between complicated and uncomplicated scrub typhus groups, but the length of hospital stay was significantly longer in complicated scrub typhus group. In clinical symptoms and signs, the frequency of pedal edema and splenomegaly in complicated group was higher than uncomplicated group. In contrast, facial puffiness was significantly higher in uncomplicated group than in complicated group. However, there was no significant difference in frequency of rash, eschar, pallor, lymphadenopathy, hepatomegaly between two groups.

Demographic and clinical characteristics of complicated and uncomplicated scrub typhus patients			
	Complicated	Uncomplicated	P value
Age, years	5.3 ^a	4.6 ^a	0.195 ^c
Sex, male/female (% , male)	54/39 (58) ^b	80/67 (54) ^b	0.596 ^d
Days of hospital stay	9.5 ^a	4.7 ^a	<0.001 ^c
Rash	12 (12.9) ^b	8 (5.4) ^b	0.055 ^d
Eschar	66 (71.0) ^b	95 (64.6) ^b	0.327 ^d

Pallor	66 (71.0) ^b	102 (69.4) ^b	0.885 ^d
Lymphadenopathy	54 (58.1) ^b	67 (45.6) ^b	0.065 ^d
Facial puffiness	72 (77.4) ^b	78 (53.1) ^b	<0.001 ^d
Pedal edema	51 (54.8) ^b	11 (7.5) ^b	<0.001 ^d
Hepatomegaly	81 (87.1) ^b	106 (72.1) ^b	0.007 ^d
Splenomegaly	42 (45.2) ^b	38 (25.9) ^b	0.003 ^d
^a values are presented as mean.			
^b values are presented as number (%).			
^c independent sample t test			
^d fisher exact test			

In complicated group, serum albumin level (normal:3.5-5.5 gm/dl) was lower and the level of alanine aminotransferase (normal: <45 IU/L), aspartate aminotransferase (normal: <45 IU/L) and alkaline phosphatase (normal:145-420 IU/L) were significantly higher than the uncomplicated group. However, there was no significant difference in the increase of total serum bilirubin and PTINR between complicated and uncomplicated group.

Liver function tests of complicated and uncomplicated scrub typhus patients			
LFT parameters	Complicated ^a	Uncomplicated ^a	p value ^b
Total serum bilirubin(mg/dl)	0.56 (0.22-0.7)	0.30 (0.21-0.41)	0.58
Alanine aminotransferase (IU/L)	89.90 (69.5-230)	47.00 (36.7-92.7)	<0.001
Aspartate aminotransferase (IU/L)	160.20 (64.3-246)	65.00 (42.4-92)	<0.001
Alkaline phosphatase (IU/L)	183.0 (107-318)	170.0 (140-217)	0.021
Total serum Albumin (gm/dl)	1.90 (1.8-2.7)	2.82 (2.1-3.45)	<0.001
PTINR	1.13 (1.10-1.21)	1.03 (0.98-1.07)	0.62

^a, values are presented as median (interquartile range)

^b, Independent sample t test

Multivariate logistic regression analysis showed that serum AST >150 IU/L (Odds ratio/OR = 7.71, 95% confidence interval/ CI = 4.13-14.38) and serum albumin <2.5 gm/dl (OR = 3.7, 95% CI= 2.14-6.455) were independently associated with complicated scrub typhus patients.

LFT Parameters	Complicated scrub typhus group		
	OR	95%CI	P- value
Serum bilirubin >2mg/dl	2.51	0.86-7.32	0.59
Serum ALT > 150 IU/L	2.4	1.29-4.67	0.226
Serum AST > 150 IU/L	7.71	4.13-14.38	<0.001
Serum ALP > 500 IU/L	2.51	0.86-7.32	0.791

Serum Albumin< 2.5gm/dl	3.7	2.14-6.455	0.002
PTINR	0.37	0.31-0.43	0.167

OR: Odds ratio, CI: Confidence interval

Discussion

Out of 240 cases diagnosed as scrub typhus, there were more male than female patients, and the female to male ratio was 0.79:1. The mean age of presentation in this study is 4.9 years and most of the patients (50%) belong to the preschooler (3-6years) and school-aged children(6-10years). The youngest infant diagnosed with scrub typhus was of 2months. Most of the cases were admitted between the months of July and October that's rainy and end of rainy season, suggesting that highest exposure to mite during this period.

The most common symptom in this study was fever. Most of the children presented with fever for 5 to 10 days (67%). Along with fever other symptoms were gastrointestinal symptoms such as vomiting (34.5%) and pain abdomen (15.8%). Respiratory symptoms were not frequently seen in this study. Only 12% of cases presented with cough. Huang et al reported cough in 50% and vomiting in 29% cases (1). A major proportion of children presented with symptoms suggestive of central nervous system involvement like, headache (4.6%), convulsions (13.8%) and abnormal behavior (2.5%). On physical examination, the most common findings were facial puffiness (62.5%) and pedal edema (25.8%). Kumar et al. reported facial puffiness and pedal edema in 63% and 60% respectively (2). Similarly, a study from Pondicherry reported edema in 60% while another from Vellore reported as 37% (3) (4). Rash was seen in 20 (8.3%) patients while in previous studies found rash in 15-90% of cases (1) (3) (5) (6).

Although presence of an eschar provides an important clinical clue in diagnosis (7), absence of it never rules out the possibility of having scrub typhus. Eschar was found in 67% of cases in this study, most of it was found in inguinal region, trunk and lower limbs. Lymphadenopathy, an important sign of scrub typhus was seen in 50.4% of cases. Hepatomegaly and splenomegaly were reported in 77% and 33.3% of cases respectively, which is in accordance with that reported in previous studies (8) (2) (9) (10). Splenomegaly is a valuable finding of scrub typhus that distinguishes it from dengue as splenomegaly is uncommon in dengue (8).

A major proportion of children in this study had anemia (69.6%) as revealed by analysis of laboratory parameters and clinical examination for pallor. Leukopenia was detected in 5% of cases and Leukocytosis in 30.4% of cases. In previous studies leukopenia was recorded in 14.7%-18% and Leukocytosis ranging from 17-28% of cases (11) (12). Thrombocytopenia, a common finding in scrub typhus, seen in 35.4% of cases which was within the reported frequency of 22-80% (8) (2) (10) (11).

The definitive diagnosis of scrub is by serology. Gold standard serological tests are immunofluorescence antibody test or indirect immune-peroxide assay (13) but are not readily available and very costly. Weil Felix test is however readily available in our country. it is highly specific but lacks sensitivity (14). In present study we used ELISA testing IgM antibody for diagnosis. This test has shown good sensitivity and specificity and had been adequately validated (84). All of the patients were treated with intravenous Doxycycline initially. Then after effervescence patients were prescribed oral formulation of doxycycline. Treatment guidelines for the cases were based on the standard textbook of pediatrics (79).

In this study, there was no significant difference in proportion of children having pallor, lymphadenopathy, hepatomegaly, presence of eschar and rash between complicated and uncomplicated

groups. The duration of hospitalization was significantly higher in complicated group. The proportion of cases with pedal edema and splenomegaly was significantly higher in complicated group when compared with uncomplicated group.

Scrub typhus is a multisystem infectious vasculitis that can cause several complications. In this study patients were classified into two groups: “Complicated scrub typhus” and “uncomplicated scrub typhus” based on presence or absence of complications. 39% of cases land up in some complications and rest were successfully discharged without any complications in present study. The most common complication observed was meningoencephalitis (16.2%), which comes in the range between 2.3% to 34.5%, as described by other studies (12) (15) (2) (16) (17). These children presented with fever, headache, irritability, nausea, vomiting and convulsions. Some of the patients had altered sensorium. CSF study in them revealed mononuclear pleocytosis with normal CSF glucose and protein. All of them recovered with treatment without any neurological deficit. Therefore, scrub typhus should be one of the differential diagnoses of meningoencephalitis with CSF mononuclear pleocytosis (16).

Another frequent complication was myocarditis (15%), which is in contrast to other studies, showing much higher incidence (2) (15). All of the patients with myocarditis in our study had muffled heart sounds, low blood pressure, and most of them presented with features of congestive cardiac failure and some with cardiogenic shock. All of them had ECG changes and cardiomegaly in chest radiograph. Shock was present in 17.9% of cases in present study. Out of them 12.5% had septic shock, and 5.4% had cardiogenic shock. In previous literatures shock was described in 25-46% of cases of scrub typhus (8) (10) (18) (19).

About 12% of cases had developed AKI in this study. Recent studies on pediatric data have reported incidences of AKI in scrub typhus ranging from 0.7% to 20% (8) (2) (10) (18). A retrospective study conducted in Chennai concluded that incidence of AKI is much less in pediatric population than adults (20). Therefore, rickettsial infections should not be overlooked as a cause of AKI in children presented with acute febrile illness. The lower incidence of AKI in this study could be due to early detection of shock, prompt management with fluids and early initiation of vasoactive drugs. Only 6 cases (2%) needed renal replacement therapy.

The incidence of respiratory complications in children with scrub typhus was less. Only 9% cases had features of ARDS and 3% developed pneumonia in this study. These clinical diagnoses were supported by abnormal chest radiographs and blood gas analysis. Review of previous studies demonstrates incidence of pneumonia in pediatric scrub typhus ranges from 3% to 31.9% and ARDS from 4% to 15.5%. The pathogenesis of ARDS in scrub typhus was described in a recent study done by Trent et al. (21). Nine percent of patients in current study developed multiorgan dysfunction (MODS) and 6% developed disseminated intravascular coagulation (DIC), which is similar to that found by previous studies (2) (8) (15).

The current study demonstrates that most of the children (88%) have some abnormalities in liver function tests. A major proportion of patients exhibited elevated levels of alanine aminotransferase (70%), and elevated levels of aspartate aminotransferase (77.9%). These findings were supported by a previous study in children (22). Several studies in adults also show similar findings (23) (24) (25). Another noteworthy observation was AST levels were more increased than ALT levels in these children, analogous observations were derived in previous studies in children as well as in adults (22) (24) (15). In contrast, acute infections with hepatotropic viruses causes more pronounced elevation in ALT than AST

(26). This suggests hepatocellular injury done by the rickettsial pathogen has some other mechanism except for direct invasion and destruction of hepatocytes. The hepatic dysfunction in scrub typhus is postulated as focal or disseminated vasculitis and perivasculitis of intra hepatic sinusoidal endothelium leading to hepatocellular damage and hence increased levels of transaminases, these findings are suggested by evidences from previous studies and immunohistological staining of hepatic tissue of patients with scrub typhus (23) (25) (27) (28). The serum alkaline phosphatase (ALP) levels were high (>500 IU/L) in 45% of cases. However, these high levels cannot be attributed to hepatobiliary dysfunction alone, as in children growth and changes in bone metabolism causes high variability of this enzyme levels (29). M. Kumar et al demonstrated an increase in ALP in 29% of cases in their study (2). Hyperbilirubinemia (Total serum bilirubin >1mg/dl) was another abnormality found in only 10% of cases in this study. Most of them were having unconjugated hyperbilirubinemia, which again suggests hepatocellular injury. Although very few cases (3%) had jaundice clinically. Another abnormal LFT parameter was hypoalbuminemia (Serum albumin <2.5 gm/dl). It is reported in 48.3% of cases in this study. However, a lower incidence of hypoalbuminemia was recorded in a previous study (22). The cause of low serum albumin is plasma leakage due to diffuse vasculitis and increased vascular permeability. This decrease in albumin levels is a transient process as the levels return to normal values in one to 4 weeks of antibiotic therapy (22). In this study 4.1% of cases had high levels of PT-INR (>1.5), in contrast to some previous studies which showed a higher rate of derangement of PT-INR levels (30) (15). A study done in adults revealed that 3.1% patients with scrub typhus had high PT-INR values (24). PT-INR, although routinely not done in LFT panel, but it is a marker of synthetic function of Liver and increase in its levels directly correlates with hepatic failure (26). Such low incidence of derangement in PT-INR values suggests that vasculitis induced hepatic dysfunction is more common in pediatric scrub typhus, rather than liver failure. Table y compares the rate of LFT abnormalities found in previous studies to current study.

After statistical analysis of various LFT parameters, it is established that serum AST, ALT and ALP are significantly high and serum albumin is significantly low in patients with complicated scrub typhus infection when compared with uncomplicated group. Similar findings were described in previous studies. In children, C. Chanta et al. demonstrated that elevated ALT, AST and hypoalbuminemia is associated with complicated scrub typhus disease (22). Similar reports were illustrated in various studies done in adults (31) (32) (33). In current study, it was documented that AST > 150 IU/L and serum albumin < 2.5 gm/dl independently predicted development of complicated scrub disease in children. Similarly, Ganesh et al. demonstrated AST levels >120IU/L has a high risk of developing complications (34). A. Alam et al. established AST levels >100 IU/L as an independent predictor of scrub typhus meningoencephalitis in children (35). Dinesh et al. demonstrated hypoalbuminemia as an independent predictor of complicated scrub in children (19).

Conclusion

Deranged liver function test is common in pediatric scrub typhus. Elevated serum AST and low serum albumin were identified as independent predictive factors of complicated pediatric scrub typhus. Therefore, these predictors could be useful for early diagnosis of complicated scrub typhus in children.

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