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Original Research Article

Clinical profile and predictors of severity in children with scrub typhus admitted to paediatric intensive care unit

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ABSTRACT

Background: Scrub typhus accounts for a significant portion of morbidity and mortality related to tropical infectious diseases. This study is done to determine the factors associated with complications and outcome in children with scrub typhus.
Methods: It is a retrospective descriptive study conducted on children diagnosed with scrub typhus (IgM) admitted to the paediatric intensive care unit at a tertiary care centre in south India during 1 year of study period. Clinical profile, laboratory parameters, course of illness and outcome data were collected and analysed.
Results: The study population included 88 children with scrub typhus. 32 children required intensive care unit admission. Remaining 56 children were included in non-severe scrub typhus group. Complications of scrub typhus included hepatic dysfunction (100%), pneumonitis 16 (50 %), meningoencephalitis 12 (37.5%), shock 12 (37.5%), acute respiratory distress syndrome (ARDS) 4 (12.5%), myocarditis 4 (12.5%), acute kidney injury (AKI) 2 (6.25%), multiple organ dysfunction syndrome (MODS) 2 (6.25%) and purpura fulminans 1 (3.1%). Mortality was observed in 2 (1.3%) children. It was found that anaemia and leucocytosis were predominantly associated with the risk of severe scrub typhus (odds ratio of 6.43 and 30.4 respectively, p value <0.001). Among other laboratory parameters, C-reactive protein (CRP) of >30 and hypoalbuminemia were significantly associated with mortality (p value <0.001). The median CRP and AST levels were significantly high in the severe scrub typhus group (p value 0.02 and 0.012 respectively).
Conclusions: Hepatic dysfunction was present in all children admitted to PICU. Children with scrub typhus had an increased risk of developing complications in the presence of anaemia, leucocytosis, CRP>30 mg/l and severe hypoalbuminemia.

Keywords: Scrub typhus, Rickettsial infections, Hypoalbuminemia, Children, Liver dysfunction

INTRODUCTION

Scrub typhus is one of the most common causes of undifferentiated febrile illness in tropical region caused by *Orientia tsutsugamushi*. The diagnosis is often delayed due to similar clinical presentation to other tropical infectious diseases like dengue fever. Mortality rate in untreated cases ranges from 10-30%.[1] Studies across the world have evaluated the risk factors associated with increased complications and mortality. However, most of them are studied in adults.[2] Very few studies are available with respect to paediatric age group. This study is done to determine clinical and laboratory parameters associated with increased severity of illness and outcome of severe scrub typhus in children.

METHODS

This is a retrospective descriptive-analytical study conducted at a paediatric unit of the department of Paediatrics of Kasturba Medical College, Manipal, located at Karnataka state in South India. The study population

included children from 1 month-18 years of age diagnosed with scrub typhus admitted during the study period of 1year from July 2018 to June 2019. The diagnosis of scrub typhus was confirmed by IgM enzyme-linked immunosorbent assay (ELISA) positivity.

Exclusion criteria included those children with scrub typhus who were simultaneously positive for other infections (dengue, malaria, typhoid fever, leptospirosis, blood culture positivity). We also excluded those where the scrub typhus based only on OX-K titre in Weil Felix test.

Data on the children diagnosed with scrub typhus was collected from the medical records department (MRD). Baseline demographic, clinical and laboratory information including haemogram and liver function test were documented. Chest X-ray and cerebrospinal fluid (CSF) examination findings were documented. Serological tests to rule out other tropical febrile illnesses such as malaria, dengue fever, leptospirosis, enteric fever and chikungunya were also done. Serum creatine phosphokinase (CPK) levels, electrocardiography (ECG) and echocardiography findings were included. Hepatomegaly was considered as liver enlargement >2 cm below the right costal margin. Anaemia was considered based on World Health Organization (WHO) cut off levels for different age groups. Leucocytosis was considered when total white blood cell (WBC) count exceeds 11,000/mm^3. Thrombocytopenia was considered if platelet count was below 150,000/cu mm. Elevated AST (aspartate amino-transferase) was defined as AST >3 times the upper limit of normal (40 IU/l). Alanine amino-transferase (ALT) >3 times the upper limit of normal (40 IU/l) was considered as elevated. Elevated serum total bilirubin (TB) was defined as TB>2 mg/dl. Hypoalbuminemia was defined as serum albumin levels <3.4 gm/dl. Severe hypoalbuminemia was considered if the serum level was <2.5 gm/dl.[3] Prolonged international normalized ratio (INR) was defined as INR>1.5.

The complications of scrub typhus were defined as follows. Hepatic dysfunction was defined as elevation of serum transaminases more than 3 times the normal upper limit (40 IU/l) or serum total bilirubin >2 mg/dl. 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 pediatric ARDS criteria.[4] Acute kidney injury (AKI) was considered as per kidney disease: improving global outcomes (KDIGO) definition and classification.[5] Myocarditis was diagnosed when the following conditions were observed: clinical findings consistent with left ventricular dysfunction, echo – presence of global left ventricular wall motion abnormality, and elevated CPK-MB levels in the blood, with or without ECG abnormalities. Meningoencephalitis was considered with the presence of altered sensorium along with meningeal signs and/or seizures along with positive CSF findings. Multiple organ dysfunction (MODS) - dysfunction of more than 1 organ requiring intervention to maintain homeostasis.

Clinical and laboratory parameters were compared between children admitted to PICU (severe scrub typhus) and those not requiring PICU admission (non-severe scrub typhus). The length of PICU stay and total duration of hospital stay were recorded. Outcome was defined in terms of mortality and survival.

Obtained data was analysed using the statistical package for social sciences (SPSS) V23.0. Descriptive data was 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 respectively. Parameters such as age, malnutrition, anemia, thrombocytopenia, elevated CRP, leucocytosis, elevated AST, hypoalbuminemia were analyzed to determine their association with severity of illness. The statistical significance was considered with a p value of <0.05.

RESULTS

Total number of children diagnosed with Scrub typhus during the study period was 94. 6 children were excluded (4 children were positive only for OX-K titre in Weil Felix test; 2 children were simultaneously positive for Leptospira IgM). Of the 88 children, 32 (36.4%) children positive for IgM scrub typhus were admitted to PICU as depicted in Figure 1.

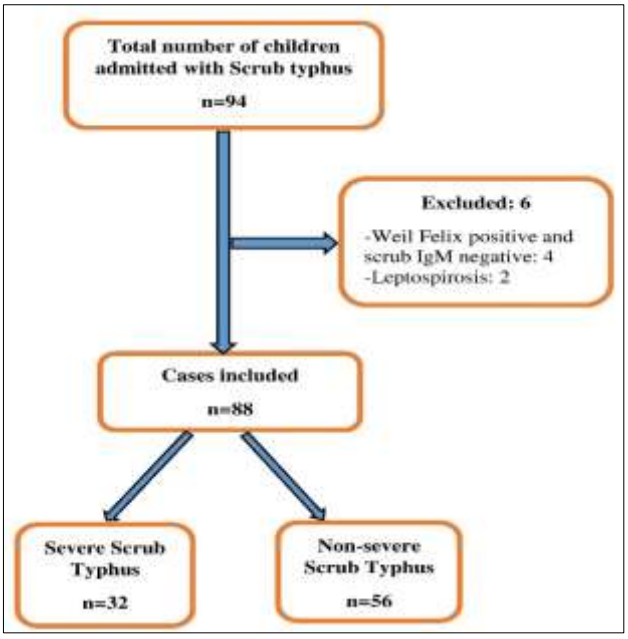

Figure 1: Study flow chart of children admitted with scrub typhus.

Mean age of the study population was 7.2±4.56 years (range 0.9-12 years), with a male: female ratio of 1.9:1. Fever was the presenting symptom in all children and 20 (62.5%) children presented with fever of >7 days duration. Symptoms and signs of children with scrub typhus are summarised in Table 1. The mean duration of illness prior to admission was 7.3±3.38 days with a range of 3-12 days. Fever was present in all children. Other common symptoms observed included vomiting (87.5%), headache (75%) and pain abdomen (46.8%). History of jaundice was present in 4 (12.5%) children. CNS symptoms such as altered sensorium and seizures were observed in 10 (31.3%) children.

Common examination findings included hepatomegaly (100%), tachycardia (100%), pallor (87.5%) and edema of peripheries (75%). Tachypnea was seen in 20 (62.5%), pulse oximetry saturation of <90% was observed in 12 (37.5%) children. Meningeal signs were present in 12 (37.5%) patients. Rickettsial rash and eschar was noticed in 6 (18.7%) and 8 (25%) children respectively.

Complications of scrub typhus were observed in 52 (36.4%) children. They included hepatic dysfunction (100%), pneumonitis 16 (50 %), meningoencephalitis 12 (37.5%), shock 12 (37.5%), ARDS 4 (12.5%), myocarditis 4 (12.5%), AKI 2 (6.25%), MODS 2 (6.25%) and purpura fulminans 1 (3.1%). Of the 12 children with shock, 8 required inotropic support while rest required fluid boluses. 14 children required oxygen/respiratory support. 8 children required non-invasive respiratory support while, 6 children required mechanical ventilation. The mean duration of PICU stay was 4.3±2.06 days (range 1-7 days). The mean duration of hospital stay was 5.2±3.12 days (range 2-12 days). Doxycycline was used in 30 (93.7%) children while 2 children with meningitis in addition received Chloramphenicol. 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 hypoalbuminemia and prolonged INR. Baseline clinical and laboratory features of non-survivors are summarized in Table 2.

Common predictors of severity of illness were compared between severe and non-severe scrub typhus groups as depicted in Table 3. It was found that anaemia and leucocytosis were predominantly associated with the risk of severe scrub typhus (odds ratio of 6.43 and 30.4 respectively, p value <0.001; Fisher exact test). Among other laboratory parameters, CRP of >30 and hypoalbuminemia were significantly associated with risk of severity (p value <0.001; Fisher exact test). The median CRP (96.2 mg/l versus 36.4 mg/l) and AST (320 IU/l versus 118 IU/l) levels were significantly high in the severe scrub typhus group (p value 0.02 and 0.012 respectively).

Table 1: Symptoms and signs of children with scrub typhus admitted to PICU.

Symptom	n=32 (%)	Sign	n=32 (%)
Fever	32 (100)	Hepatomegaly	32 (100)
Vomiting	28 (87.5)	Tachycardia	32 (100)
Headache	24 (75)	Pallor	28 (87.5)
Pain abdomen	15 (46.8)	Oedema	24 (75)
Swelling of limbs	14 (43.7)	Tachypnea	20 (62.5)
Hurried breathing	12 (37.5)	CFT<3 sec	18 (56.2)
Abdominal distension	10 (31.3)	SpO_2<90%	12 (37.5)
Altered sensorium	10 (31.3)	GCS<15	12 (37.5)
Seizures	10 (31.3.)	Meningeal signs	12 (37.5)
Jaundice	04 (12.5)	Hypotension	11 (34.4)
		Ascites	10 (31.3)
		Splenomegaly	10 (31.3)
		Eschar	8 (25)
		Skin rash	6 (18.7)
		Icterus	4 (12.5)

Table 2: Baseline clinical and laboratory features of non-survivors.

S. no.	Parameter	Case 1	Case 2
1	Age	4 years 8 months	12 years
2	Gender	Female	Male
3	Duration of illness (days)	12	10
4	Underlying comorbid illness /risk factor	Grade 1 malnutrition	BMI <3rd centile
5	Laboratory findings	Anaemia (Hb 9.2 g%, thrombocytopenia (80,000/mm^3),	Anaemia (Hb 10.4 g%, thrombocytopenia (1.2 lakhs), elevated

Continued.

S. no.	Parameter	Case 1	Case 2
		leucocytosis (15600/mm^3), elevated CRP (86 mg/l), elevated D-dimer (2 ng/ml), AST 1560 U/l, ALT 660 U/l, hypoalbuminemia (2.2 g/dl)	CRP (120 mg/l), elevated D-dimer (1.6 ng/ml), elevated AST (360 U/l), ALT (220U/l), hypoalbuminemia (2.8 g/dl)
6	Complications	Meningoencephalitis, MODS (respiratory failure, septic shock, AKI)	ARDS, refractory shock, MODS, AKI

Table 3: Comparison of predictors of severe illness between scrub typhus groups.

Parameter	Severe scrub typhus (n=32)	Non-severe scrub typhus (n=56)	OR [95% CI]	P value
Malnutrition (n=24)	8	16	0.83 [0.26, 2.45]	*0.87
Anaemia (n=36)	22	14	6.43 [2.29, 19.41]	*<0.01
Mean haemoglobin (g/dl)	8.42±1.54	10.22±1.57		#0.55
Leukocytosis (n=48)	30	18	30.4 [6.55, 287.64]	*<0.001
Median TLC (x10^9 cells/l) (IQR)	11700 (6300;16800)	8,700 (4600;13600)		##0.34
Thrombocytopenia (n=48)	20	28	1.65 [0.63, 4.48]	*0.27
Median platelet (x10^9 cells/l) (IQR)	90 (32;220)	96 (44;360)		0.21
CRP >30 mg/l (n=42)	28	14	20.09 [5.70, 98.20]	*<0.001
Median CRP (IQR)	96.2 (32.02;182.2)	36.4 (12.52;.76.4)		##0.02
Elevated AST (n=68)	28	40	2.27 [0.77, 12.63]	*0.114
Median AST (IU/l) (IQR)	320 (98, 540)	118 (66, 246)		##0.012
Severe hypoalbuminemia (<2.5 g/dl) (n=18)	16	2	25.78 [5.24, 253.3]	*<0.001
Mean serum albumin ±SD (g/dl)	2.82±0.74	3.56±0.64		#0.04

*Fisher exact test, #Independent sample t-test, ## Mann-Whitney U test, OR [95% CI] - odds ratio, 95% confidence interval

DISCUSSION

Scrub typhus is a recognized cause of severe illness with multi-organ dysfunction related to tropical infectious disease. Other tropical infectious diseases attributed to organ dysfunction include malaria, dengue fever, leptospirosis and typhoid fever. Most of these illnesses initially present with undifferentiated fever (often >5 days). Though skin rash and eschar are specific for scrub typhus, the prevalence rate is low ranging from 8-15% as reported in a study conducted by Sivarajan et al from Meghalaya.[6] In the present study we included children who are only positive for IgM scrub typhus ELISA, as Weil Felix is a nonspecific test for the diagnosis of scrub typhus. Though indirect immunofluorescent antibody (IFA) test is the gold standard, however it is expensive and not easily available in many centres.[6,7]

Factors associated admission to PICU in the present study included respiratory distress, hypoxaemia, altered sensorium and presence of shock. Similarly, in a prospective study done by Khemka et al in Eastern India, it was found that respiratory distress, altered sensorium, convulsion, and shock are the common indications for PICU admission.[7] According to a retrospective observational study conducted by Nallasamy et al from Chandigarh, India, the presence of lymphadenopathy, respiratory distress, shock, elevated lactate, and meningo-encephalitic presentation were the independent predictors for the need of intensive care.[8]

The main pathophysiology in scrub typhus is involvement of endothelial cells that initiates the release of pro-inflammatory cytokines like TNFα and CXCL8 (IL-8), this further leads to recruitment of leukocytes and chemokines leading to micro vascular injury in liver, brain, lungs, kidneys leading to multi-organ dysfunction.[9] Hence elevated markers of inflammation like leucocytosis, high CRP and elevated AST levels predict increased risk of organ dysfunction and mortality.

Common complications described in the literature include severe thrombocytopenia with bleeding diathesis, meningoencephalitis, pneumonia, ARDS, disseminated intravascular coagulation (DIC), AKI, myocarditis and purpura fulminans. Hepatic dysfunction with acute liver failure is a common complication associated with MODS. Majority of studies conducted in India have reported high prevalence of central nervous system involvement.[9] Gurunathan et al also reported bleeding manifestation, altered level of consciousness, AKI, seizures (manifestation of febrile seizure meningoencephalitis) and visual disturbances in 18.5%, 18.5%, 10.8%, 10% and 6.9% of the study population respectively.[10] Though relatively rare, secondary haemophagocytic lympho-histiocytosis (HLH) has been reported as a well-recognized complication of scrub typhus in children. However, none of the children in the present study were diagnosed with HLH secondary to scrub typhus.[11]

Various risk factors reported to be associated with severe illness in scrub typhus include malnutrition, anemia, and shock at admission, leucocytosis, high CRP and elevated hepatic transaminases. In a study by Narayanasamy et al on multiple logistic regression analysis, 5 factors namely, breathlessness, altered sensorium, leucocytosis, hypoalbuminemia and hyponatremia were found to be significantly associated with severe scrub typhus.[12]

The prevalence of hepatic dysfunction varies in different studies. Previous studies have demonstrated that the prevalence of serum aminotransferase elevation ranges from 34% to 96%.[13-15] In the present study liver dysfunction was present in all children with scrub typhus admitted to PICU. In a study done by Chanta et al in Thailand, it was found that increased AST, ALT, and hypoalbuminemia were associated with severity of illness.[13] It was also concluded that raised AST can be used to diagnose scrub typhus in the absence of a rapid diagnostic serological test. 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 4 (12.5%) children. In other studies, elevated total serum bilirubin is also considered as marker of severe illness and prevalence ranges from 7.4% to 19.7%. [16]

Severe hypoalbuminemia was found to be significantly associated with an increased risk of complications in the present study which was comparable to previous studies.[17] Children with complications were observed to have low mean serum albumin (2.28±0.74 versus 3.56±0.64) and was statistically significant (p=0.04). Severe hypoalbuminemia was present in both non-survivors in the study.

Doxycycline is the mainstay of treatment for scrub typhus. Recommended dose in 4-4.5 mg/kg/day in 2 divided doses for and for >40 kg body weight, 100 mg twice daily for 7-10 days.[18] In severe cases IV doxycycline can be used. In the present study, doxycycline was used in 30 (93.7%) children. Chloramphenicol was used in 2 children with meningoencephalitis in addition to doxycycline as it has better penetration through blood brain barrier.

Limitations of the study include its retrospective nature and limited sample size. This is a single centre study where data was collected for children admitted over a period of 1 year. Multicentric prospective studies would be better to evaluate risk factors for admission to pediatric intensive care unit and assess the severity of illness and outcome.

CONCLUSION

The clinical presentation, complications and outcome of children with severe scrub typhus is described in the study. Anaemia, leucocytosis, elevated CRP >30 mg/l, raised AST >3 times and severe hypoalbuminemia were found to be significant predictors of complications and organ dysfunction. Hence in the presence of these factors, close observation and intensive care monitoring to prevent complications is essential. Demerits of the study include limited sample size and retrospective nature. Further prospective multi-centric studies are needed to identify.

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