



PREVALENCE OF SCRUB TYPHUS AND DIFFERENTIATION FROM OTHER FEBRILE ILLNESSES IN CHILDREN IN UTTAR PRADESH, INDIA

Paediatrics

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ABSTRACT

Objectives: i) To compute prevalence of scrub typhus (ST) in AUFU in children presenting to a public teaching hospital in Uttar Pradesh, India and ii) delineate differentiating features from ST negative patients

Methods: First 3 consecutive children with AUFU seen as outpatients or admitted on 2 predecided week days who consented for study were enrolled. IgM against ST was tested by commercial ELISA kits. Demographic, clinical and laboratory features were compared between ST positive and negative patients by univariate followed by logistic regression analysis to reach significant independent 'predictors' of the diagnosis.

Results : A total of 138 AUFU patients were enrolled of which 29 (21%) were ST IgM positive. Headache, vomiting, tachypnea, season, rash and low serum albumen were significant independent predictors of the diagnosis.

Conclusions: ST is an important cause of AUFU in children in Uttar Pradesh. The diagnosis can be predicted by certain clinical / laboratory features.

KEYWORDS

acute undifferentiated febrile illness, scrub typhus, sensitivity, specificity, logistic regression

INTRODUCTION

Acute febrile illness is the medical term used to describe a sudden fever or elevation in body temperature. Fever can be caused by infectious and noninfectious pathology. However the most important cause is infectious etiology. Infectious agent may be a recognizable bacterial, fungal, viral, protozoal, metazoal, rickettsial or mycoplasma infection. The term acute undifferentiated febrile illness (AUFU) connotes an acute illness with fever without any evidence of organ or system specific etiology [1]. A specific focus of infection is not found. In developing countries causes of AUFU are varied and include tropical infections like Dengue, Chikangunya, typhoid, malaria leptospirosis, spotted fever rickettsioses and Hanta virus etc [2].

Among AUFU one cause is the rickettsiosis - Scrub typhus (ST), which is gaining importance. Over the last five years, with the availability of the IgM ELISA test, there are many reports of this illness from south, central and north eastern India. In 2012, the National Centre for Disease Control (NCDC) confirmed a multi-state outbreak of ST.

Uttar Pradesh is India's most populous state (with a population of more than 200 million, about 1/6th of that of the whole country) and also one of its poorest with lowest human development indices. It is divided into 70 districts or administrative units. This part of the country is the gangetic plain of northern India. The state's population density is 689 people/sq km and children below 15 years account for roughly 40% of the population. About 79% of the people live in rural areas. The eastern parts of the state are poorer, less developed and largely rice growing. The countryside is sprinkled with villages – population ranging from 1000-5000 per village. There are 3 seasons – summer (March to June), rainy or monsoon season (July to October) and winter (November to February). Temperatures may soar up to 45 °C in summer and fall as low as 3 °C in winter. During and after the monsoon, the rice fields as well as large areas around the villages are waterlogged. Lucknow is the capital city of Uttar Pradesh and has a population of 4 million. The King George Medical University (KGMU) Hospital in Lucknow is a tertiary care teaching hospital here, which caters mostly to the poor and severely ill. The catchment area of the hospital includes the Lucknow city and district and mostly eastern districts extending upto Nepal.

There is only one report implicating ST as a cause of fever in Uttar

Pradesh, and none in children. We therefore proposed to study the prevalence of scrub typhus in children presenting with AUFU in a public teaching hospital in north India and further to describe the clinical and laboratory features of scrub typhus and identify the distinguishing features from other causes of AUFU, so that it can be suspected and treated promptly, even in peripheral areas where diagnostic facilities are not available.

PATIENTS & METHODS

Over a period of one year between September 2016 to August 2017, children between 6 months and 14 years seen in pediatric OPD or admitted in pediatric wards of King George's Medical University, Lucknow were screened for enrollment in the study. They were enrolled if their main complaint was fever with duration of upto 14 days and cause of the fever was not evident from clinical history and examination. Only the first 3 such children attending OPD or admitted on two predecided week days were enrolled if the parent or guardian gave consent for the study. Children with seizures or altered sensorium were excluded.

At first contact, a detailed clinical evaluation was done and entered on predesigned data collection forms. Special effort was made to look for the typical 'eschar' and any rash. Laboratory work up included complete blood counts including platelets, renal function tests - s.urea and s. creatinine, serum electrolytes, rapid malaria test and peripheral smear for malarial parasite, liver function tests - serum bilirubin, ALT, AST, serum alkaline phosphatase, total protein, albumin and prothrombin time, urine routine and microscopy, urine culture and sensitivity, blood culture and sensitivity, Widal test and chest X Ray.

In addition 3-5 ml of blood was transported to the Microbiology Department of KGMU for the following tests : i) Serum IgM ELISA for *O. tsutsugamushi* using commercial kit Scrub Typhus Detect (InBios International Inc., Seattle, WA, USA) as per the manufacturer's instructions. An optical density (OD) >0.5 was considered positive [3]. A positive IgM ELISA test was considered as evidence of ST infection.

Sample size was computed as for a prevalence study with dichotomous outcome using the formula $N = 4z^2 P(1-P)/W^2$ where P is the expected proportion, z is the standard, normal deviate and W is

the total width of confidence interval. With P taken as 10% and W as 0.1, z_{α} as 1.96, sample size came to 140 patients approximately [4].

Analysis: Demographic data, history, examination and investigations were entered in an Excel spreadsheet. Statistical analysis was performed using EPI-INFO version 7.2 for Windows. Primary outcome was a positive IgM ELISA test for ST. Prevalence of scrub typhus among cases of AUFI was computed. Clinical features of ST AUFI were described and compared to patients without evidence of ST. ANOVA or 2 sample t test were used for continuous variables and Chi square test was used for categorical variables on univariate analysis. Variables with p value of < 0.05 were entered in a logistic regression model by standard methods to arrive at significant independent predictors of the diagnosis of ST.

Ethical Approval was obtained from King George's Medical University Ethics Committee. Written informed consent was taken from parent/guardian. The study was purely observational.

RESULTS

A total of 142 patients were screened for the study, out of which 4 patients were excluded, so total enrolled were 138. Twenty nine of these patients were positive for IgM against ST. The prevalence of ST was therefore 21%. Demographic and clinical features were compared between the ST positive and negative cases and are shown in Table 1.

History of headache and vomiting, presence of swelling over the body, rash, lymphadenopathy, palpable spleen, and hepatomegaly were all significantly more common in ST positive group. Swelling was in the form of non pitting edema all over the body but especially noted on the face. Involvement of respiratory system with tachypnea was also significantly more frequent in ST positive group.

Table 2 shows the comparison of laboratory parameters between ST positive and negative patients. It is seen that mean total leucocyte counts and blood urea were significantly higher in ST positive patients, while mean platelet counts, total serum protein and serum albumen were significantly lower.

Table 3 shows the results of logistic regression analysis, in which the final model included 6 variables – headache, vomiting, tachypnea, season, rash and low serum albumen.

DISCUSSION

Fever is a common reason for seeking healthcare in low- and middle-income countries (LMICs) [5]. Infection is the most common cause of fever and therefore a systematic search for a focus of infection must be made by history, examination and investigation. Many a times no focus can be found, and the term acute undifferentiated febrile illness (AUFI) is used. The cause of AUFI is driven by the regional disease burden, seasonality of infectious diseases, spectrum and severity of disease, availability of diagnostics and access to health care facilities. The relative prevalence of different etiologies for the AUFI varies with the geographic region. In tropical low and middle income countries, important causes are Malaria, dengue, tuberculosis, typhoid, fever, brucellosis etc. In addition, ST has been reported from all over the country [6] over the last few years. Although being the largest state of India in terms of population, Uttar Pradesh has no such study in children.

Strengths of our study were that we have compared ST positive and negative group based on clinical and laboratory features, to get significant difference between these two groups. This approach was not followed in previous studies in which only features of ST positive group have been described. IgM ELISA for scrub typhus was used which is an acceptable test with good sensitivity and specificity. Most of the patients enrolled in our study were hospitalized, thus they could be followed up daily till discharge. Enrollment was unbiased because we included all children seen on 2 predecided week days. Logistic regression was done so as to get significant independent 'predictors' of the diagnosis. This information would be useful to physicians working in peripheral resource poor areas to suspect the diagnosis even without the specific laboratory diagnosis. Limitations include firstly that patients were those seen in a tertiary care referral hospital and may not represent the true situation in the community. Second, for about 51% of the patients, diagnoses was not made.

The prevalence of ST among cases of AUFI was 21%. For a single etiology this is very high. In various parts of the country since 2010, prevalence has ranged from 13.5% to 30.7%. Most of our patients were of rural origin, which may simply reflect the population our hospital caters to. As shown in fig. 1 most of the people were from districts to the north east of Lucknow. In the present study 26/29 (89.6%) patients were positive in the months of July to December (Figure.2). Khan et al (2015) reported that the maximum number of scrub typhus cases came in the months of August to October each year [7], while Khandelwal et al (2015) reported that 37 cases (71%) were seen between September and November which are the post monsoon months [8]. Vivekanandan et al (2010); Mahajan et al (2006); Varghese et al (2006); Oberoi et al (2014) and Kamarasu et al (2007) have also reported the post monsoon outbreak of the disease [9,6,10,11,12].

The most common clinical features observed in our patients were headache, vomiting, swelling, hepatomegaly and tachypnea. All these symptoms were seen in higher proportion of our patients than in earlier studies. An eschar (Figure.3) was found in 6.9%, which is similar to the other Indian studies with eschar being found in (8–15%) in ST. Mahajan et al (2008); Sinha et al (2014) reported eschar to be 0% in their studies. [13,14]

We found that mean blood leucocyte count was higher in ST positive group and this was statistically significant. Total leucocyte count in blood is generally believed to be low in ST. However other workers from India (Varghese et al, 2006; Chandra et al, 2017) also found leucocytosis in upto 75% [10, 15]. Thrombocytopenia was a consistent laboratory feature in ST and was found in more than half of our patients. Kumar et al (2014) reported thrombocytopenia in 61% [16], Khandelwal et al (2015) in 88.4% patients [8] and Rama et al (2015) in 56% of their patients [17]. Mean blood urea, but not serum creatinine was found to be statistically significantly higher in ST. This was similar to other studies. Takhar et al (2017) reported renal complications in 51.5% [18]. Kumar et al (2012) reported renal abnormalities in 82% [19]. Mean serum albumin was statistically significantly lower in scrub typhus group. This was consistent with previous work. Kumar et al (2012) found hypoalbuminemia in 55% of patients [19], and Chandra Dev et al (2017) in 53.1% [15]. Low serum albumin and leucocytosis are thought to be associated with severe ST [20,21]. We did find elevated liver transaminases in our study but the ST negative group had higher mean levels, although this was not statistically significant. This is because our ST negative group was probably a mixed bag of other tropical infections – dengue, malaria, enteric fever etc which may also affect the liver. Khandelwal et al (2015) reported raised sGOT in 94.2% of patients, and raised sGPT in 78.8% of patients [8] while Chandra et al (2017) reported elevated transaminases in 81.3% of the patients [16]. The central pathophysiological derangements, liver function, renal function and thrombocytopenia in ST is because of wide spread vasculitis and perivasculitis of these organs, due to multiplication of the organism in the endothelial cells lining the small blood vessels. Thus ST can be considered a multisystem disease with involvement of skin, lungs, liver, kidney, brain and blood.

We went on to analyse our data further by multivariate logistic regression to look for the significant predictors of the diagnosis of ST. This approach eliminates the effect of confounding and co-variables to arrive at those variables which independently account for the diagnosis. Our final model had 6 variables – presence of headache, vomiting, season, rash, tachypnea and low serum albumin which 'predicted' the diagnosis of scrub typhus. This information can be used to construct a clinical prediction rule for ST. In a study in adults, Varghese et al [10] found that a combination of leucocytosis, low platelets and raised transaminases had a sensitivity of about 80%. Our results would be applicable to other regions of the world which are similar in climate and income.

In conclusion, our study shows a high positivity for ST among children presenting with AUFI in Uttar Pradesh. Headache, vomiting, post monsoon season, rash, hepatomegaly and low serum albumen were significant independent predictors of the diagnosis, which may help physicians working in peripheral to suspect/ diagnose ST.

Figure 1 District wise distribution of scrub typhus positive patients



Figure 2 Month wise distribution of enrolled and IgM scrub typhus positive patients

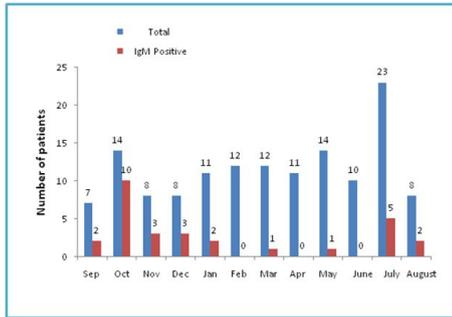


Figure 3 Eschar of Scrub Typhus in trunk region



Table 1: Comparison of demographic and clinical features between scrub typhus IgM +ve and -ve patients

Parameters	Scrub typhus IgM		OR (95% CI)	P
	Positive (29) N (%)	Negative (109) N (%)		
Age >6 months to <= 2 years	5(17.2)	22(20.2)	-	λ 0.029 p = 0.865
Age >2 years and <=5 years	10(34.5)	37(33.9)		
Age >5 to <=8 years	7(24.1)	22(20.2)		
Age >8 years	7(24.1)	28(25.7)		
Season				
January – June	3(10.3)	62(56.8)	11.4 (3.2-40)	0.000*
July – December	26 (89.6)	47(43.1)		
Sex				
Male	19 (65.5)	70 (64.2)	0.94 (0.3-2.2)	1.000
Female	10 (34.5)	39 (35.8)		
Residence				
Rural	27 (93.1)	99 (90.8)	1.36 (0.3-9.6)	0.698
Urban	2(6.8)	10 (9.2)		
Clinical features				
Headache	27 (93.1)	69 (63.3)	7.8 (1.7-34.6)	0.004*
Mean (SD) duration of fever in days	8.93 (2.80)	8.79(2.97)	-	0.817
Vomiting	23 (79.3)	49 (45.0)	4.6 (1.7-12.4)	0.002*

Swelling	20 (69.0)	45 (41.3)	3.1 (1.3-7.5)	0.010*
Eschar	2 (6.9)	0	-	0.200
Rash	13 (44.8)	20 (18.3)	3.6 (2.9-17.6)	0.006*
Pallor	18 (62.1)	46 (42.2)	2.2 (0.9-5.1)	0.080
Icterus	5 (17.2)	13 (11.9)	1.5 (0.5-4.7)	0.315
Significant Lymphadenopathy	16 (55.2)	14 (12.8)	8.3 (3.3-21.0)	0.000*
Hepatomegaly	27 (93.1)	42 (38.5)	21.5 (4.8-95.2)	0.000*
Palpable spleen	8 (27.6)	10 (9.2)	3.7 (1.3-10.6)	0.020*
Tachypnea	23 (79.3)	50 (45.8)	4.5 (1.7-12)	0.002*

Chi square test was used to compare categorical data, and 2 sample t test for continuous variables ; * Significant at < 0.05; CI - confidence Interval

Table 2 Comparison of laboratory parameters between scrub typhus positive and negative patients

Parameters	IgM Positive (N=29)		IgM Negative(N=109)		P
	Mean	SD	Mean	SD	
Hemoglobin (gm/dl)	9.4	1.4	9.9	1.9	0.202
Total leucocyte count (per cumm)	19193.5	9970.9	15114.3	6569.3	0.009*
Percentage polymorphs in leucocytes	66.8	8.8	65.1	11.3	0.441
Platelets in lacs/ cu mm	0.73	0.4	1.6	1.2	0.000*
International Normalised ratio (INR)	1.4	0.4	2.0	6.1	0.572
s.Bilirubin (mg/dl)	1.06	0.9	0.8	0.8	0.078
s.AST (IU/L)	108.8	75.6	84.7	166.9	0.451
s.ALT (IU/L)	139.7	113.2	95.5	188.4	0.231
s.Albumin (gm/dl)	2.6	0.5	2.8	0.5	0.011*
Total s Protein (gm/dl)	5.5	1.1	6.4	4.6	0.018*
Blood Urea (mg/dl)	55.6	39.6	32.9	15.6	0.000*
s Creatinine (mg/dl)	0.8	0.43	0.8	2.4	0.991

Student t test was used to compare means * Significant; SD – standard deviation

Table 3 :Unconditional Logistic Regression

Term	Odds Ratio	95% C.I.	Coefficient	S. E.	Z -Statistic	P-Value
Headache	10.5563	1.7478, 63.7560	2.3567	0.9175	2.5685	0.0102
Rash	11.0068	2.5326, 47.8358	2.3985	0.7496	3.1996	0.0014
Tachypnea	12.7761	3.1408, 51.9710	2.5476	0.7159	3.5586	0.0004
S_Albu	0.0568	0.0096, 0.3362	-2.8675	0.9069	-3.1619	0.0016
Season	0.0963	0.0244, 0.3802	-2.3401	0.7006	-3.3404	0.0008
Vomiting	17.4821	3.3967, 89.9775	2.8612	0.8359	3.4228	0.0006
CONS TANT	*	*	*	1.0829	2.0295	0.5336

Figure 1 District wise distribution of scrub typhus positive patients



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