DOI: 10.7860/JCDR/2022/57061.16778

Original Article

Paediatrics Section

Clinicolaboratory Profile and Outcome of Serologically Confirmed Scrub Typhus among Children from Sub Himalayan Tribal District of India: A Hospital-based Cross-sectional Study

RAJ KUMAR SOORYA[1], MANGLA SOOD[2], DEEPIKA DHIMAN[3]

ABSTRACT

Introduction: Scrub typhus is transmitted by the bite of the larva (chigger) of a microscopic trombiculidae mite (*Leptotrombidium*) found in moist areas and vegetation, which serves as both vector and reservoir. Scrub typhus is an often neglected and misdiagnosed febrile illness; clinical suspicion is the only key to diagnosis.

Aim: To study clinicolaboratory profile and outcome of serologically confirmed scrub typhus in children from sub Himalayan tribal district of India.

Materials and Methods: This cross-sectional observational study was conducted in Department of Paediatrics at Government District Hospital, Chamba, Himachal Pradesh, India, from May 2019 to April 2020. Children upto 18 years admitted with positive Immunoglobulin M (IgM) antibodies for scrub typhus were enrolled. The observational data including detail history and examination, relevant laboratory investigation and treatment was analysed by Statistical Package for Social Sciences (SPSS) software version 18.0 and Chi-square test with p-value <0.05 was considered statistically significant.

Results: There were total 55 patients with scrub typhus, mean age was 9.2 years, most common age group was 7-12 years, 51% were male. Fever was most common complaint, followed by vomiting (27.3%), abdomen pain (25.4%), respiratory (1.8%), and rash (9%). Clinical examination findings were generalised lymphadenopathy in 46 (83.6%) patients and splenomegaly in 29 (52.7%). Eight patients presented with respiratory signs and tachypnea at the time of admission. Eschar was present in only 3 (5.5%) patients. Sign of meningeal irritation was present in 4 (7.3% cases and low GCS score (below 9) was observed in 7 (12.7%) patients. Eight patients required mechanical ventilatory support. Nineteen patients were prescribed doxycycline alone; while 34 were given both azithromycin and doxycycline. There were total five deaths; on multivariate logistic regression, respiratory complaint, need for mechanical ventilation, pain abdomen with liver damage, history of seizures and duration of fever more than four days before presentation to hospital were associated with adverse outcome.

Conclusion: The prevalence of scrub typhus is considerably high during rainy season, and should be considered as a differential diagnosis of fever among children in this period regardless of the presence of an eschar. Immediate medical care, treatment with doxycycline with early defervescence of fever reduce mortality.

Keywords: Azithromycin, Child, Chigger, Doxycycline, Eschar, Prevalence, Trombiculidae

INTRODUCTION

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi* a Gram negative, obligate intracellular pleomorphic bacterium. It is transmitted by the bite of the larva (chigger) of a microscopic trombiculidae mite (*Leptotrombidium*) found in areas with plenty of moisture and scrub vegetations, which serves as both vector and reservoir [1]. Normally the chigger feeds on rodents (rats and mice), man is the accidental host. The disease is particularly distributed over a very wide area of 13 million km square of the world known as tsutsugamushi triangle [2]. The lungs, heart, liver, spleen, and central nervous system are all affected by focal or disseminated vasculitis and perivasculitis [3].

The incubation period is 10-12 days (range 6-21days). Clinical manifestation of the disease ranges from mild to severe in children [4]. Diagnosis require high index of suspicion, majority of the patients present with fever of 9-11 days duration along with non specific manifestations like generalised maculopapular rash and regional or generalised lymphadenopathy, hepatomegaly or splenomegaly, headache, pain abdomen, vomiting, abnormal bleeding and seizures [1]. If treatment is delayed, complications like jaundice, pneumonitis, Acute Respiratory Distress Syndrome (ARDS), septic shock, renal failure, myocarditis, meningoencephalitis and rarely Multiorgan Dysfunction Syndrome (MODS) can lead to high mortality after the first week of illness. Authors conducted this study since there was no data about scrub typhus among feverish paediatric patients in the remote majority tribal district of Chamba in the North Indian sub-Himalayan state of Himachal Pradesh.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in Department of Paediatrics at Government District Hospital, Chamba, Himachal Pradesh, India, from May 2019 to April 2020. Ethical clearance was obtained from institute IEC committee prior to enrollment (IEC/GMC/CBA/018/2019).

Inclusion criteria: All patients upto the age of 18 years who presented to the Outpatient Department (OPD), Emergency Room, or were admitted to the Paediatric Ward of the hospital with fever, sign symptoms and were serologically confirmed for scrub typhus were included in the study.

Exclusion criteria: All febrile patients who tested negative for antibodies were excluded from the study.

Study Procedure

After obtaining written informed consent from parents/caregivers, all patients fulfilling inclusion criteria were serologically confirmed

by Inbios Scrub typhus Detect™ IgM antibody Enzyme-Linked Immunosorbent Assay (ELISA) kit test (used by the Microbiology Department of hospital) were included. This kit uses recombinant p56kD antigen of Orientia tsutsugamushi TA716 strain to detect scrub typhus IgM antibodies. All sera were tested at a 1:100 dilution and the results read at 450 nm using a microplate reader (Thermo Scientific™ Multiskan™ FC) to give a final Optical Density (OD) result (at 450 nm). ELISA OD cut-off value more than one is equivalent to an IgM Indirect Immunofluorescence Assay (IFA) titre ≥3200 [5].

Total 55 patients were enrolled among 230 febrile patients during the study period. Following enrollment, a detailed history was taken, along with a physical examination, necessary laboratory tests, and treatment information. Treatment was initiated with doxycycline as 1st drug, azithromycin was added as 2nd drug along with management of patient co-morbidity and sickness as determined by the hospital's pediatric intensive care protocols. The data of rainfall was obtained from the director, Metrological Department at Shimla, Himachal Pradesh [Table-Fig-1] [6].

Month and year	Rainfall in mm
May 2019	93.7
June 2019	196.3
July 2019	296.9
August 2019	338.4
September 2019	159.4
October 2019	19
November 2019	0
December 2019	17
January 2020	11
February 2020	9
March 2020	4
April 2020	4

[Table/Fig-1]: Average monthly rainfall data of the district (source Meteorological Department of Government) [6].

STATISTICAL ANALYSIS

Data was collected on Microsoft excel, statistical analysis was done on Statistical Package for Social Sciences (SPSS) software, version 18.0 (SPSS Inc., Chicago, IL). All categorical variables were expressed as percentages, and continuous variables as mean±SD. The association and difference in distribution was analysed using Chi-square test and p-value of <0.05 was considered statistically significant.

RESULTS

Total 55 patients, 28 (50.9%) males with positive IgM ELISA for scrub typhus were included during the study period. Sixteen (29.1%) were in the age group of 1-6 year, 28 (50.9%) were in 7-12-year age group and 11 (20%) were in 13-18-year age group. Maximum number of cases 32 (58.2%) presented in the month of August, 21 (38.2%) in September and 2 (3.6%) in October. There were no patients in winter months. The frequency of cases presented matched with the level of rainfall in the area. Presenting complaints and clinical features on examination presented in [Table/Fig-2].

Total 46 (83.6%) patients presenting with generalised lymphadenopathy, 21 had generalised tender lymphadenopathy. Shock at admission was present in 13 (23.6%), only one patient presented with hypertension. Twenty nine (52.7%) patients had splenomegaly, 18 (32.7%) had hepatomegaly, 14 (25.5%) had both hepatosplenomegaly. Eight (14.5%) patients presented with respiratory sign and tachypnea at the time of admission. Low GCS score (below 9) was observed in 7 (12.7%) cases, sign of meningeal irritation was present in 4 (7.3%) cases.

Variables	n, %
Age in years	
1-6	16 (29.1%)
7-12	28 (50.9%)
13-18	11 (20%)
Month	
August	32 (58.2%)
September	21 (38.2%)
October	2 (3.6%)
Symptoms	
Fever	55 (100%)
Vomiting	15 (27.3%)
Pain abdomen	14 (25.4%)
Headache	10 (18.9%)
Cough	9 (16.4%)
Myalgia	6 (10.9%)
Rash	5 (9%)
Sore throat	4 (7.3%)
Bleeding	3 (5.5%)
Seizure	2 (3.6%)
Dyspnoea	1 (1.8%)
Clinical examination finding	
Generalised lymphadenopathy	46 (83.6%)
Splenomegaly	29 (52.7%)
Hepatomegaly	18 (32.7%)
Hepatosplenomegaly	14 (25.5%)
Fever	44 (80%)
Pallor	21 (38.2%)
Petechiae	8 (14.5%)
Rash	3 (5.5%)
Eschar	3 (5.5%)
Jaundice	2 (3.6%)
Lab investigations	
Low Hb	40 (72.8%)
Leucocytosis	17 (30.9%)
Leucopenia	3 (5.5%)
Thrombocytopenia	17 (30.9%)
Raised serum urea (>40 mg/dL)	9 (16.4%)
Raised serum Cr (>1.5 mg/dL)	39 (70.9%)
Abnormal liver function test with transaminitis	1 (0.02%)
Treatment	
Doxycycline	19 (34.6%)
Azithromycin	2 (3.7%)
Both Doxycycline+Azithromycin	34 (61.9%)

[Table/Fig-2]: Clinical presentation with laboratory investigations of patients.

Laboratory: Anaemia (haemoglobin <11 gm/dL) was detected in 40 (72.8%), thrombocytopaenia with platelet counts <1.5 lakh/mm^3 in 32 (58.2%) cases, 17 (30.9%) had leucocytosis (total leucocytes counts 11000/cumm), and leucopaenia was documented in 3 (5.5%). Only one patient had raised serum creatinine >3 mg/dL. Increased Serum Glutamic Oxaloacetic Transaminase (SGOT) was found in 39 (70.9%) patients, raised Serum Glutamic Pyruvic Transaminase (SGPT) was found in 31 (56.4%) patients, raised serum Alkaline Phosphatase (ALP) was found in 8 (14.5%) patients. Hypoproteinaemia (serum protein <5.5 gm/dL) was found in only 1 (1.8%) patient. Hypoglycaemia (random blood sugar <60 mg/dL) was detected in 2 (3.6%) patients at the time of admission.

Radiology: On chest X-ray examination of the patients, 9 (16.4%) had findings suggestive of Acute Respiratory Distress Syndrome (ARDS).

Treatment: Out of total 55, 19 patients were prescribed doxycycline; two azithromycin and 34 patients were given both these drugs. Eight (14.5%) patients required mechanical ventilatory support. There were 5 (9.1%) deaths (all deaths due to MODS with shock).

Factors associated with mortality among admitted patients were respiratory symptoms as chief complaint, shock with hypotension, hypoglycaemia, pain abdomen with hepatomegaly and signs of liver damage, deranged renal function test at admission, low Glasgow coma scale, history of seizures, and long duration of fever more than five days before presentation to the hospital. However, on multivariate logistic regression, only respiratory complaint and need for mechanical ventilation, pain abdomen with liver damage, history of seizures and duration of fever more than four days before presentation to hospital, defervescence of fever more than four days after admission were all associated with adverse outcome as death among five patients [Table/Fig-3].

S. No.	Variable	Alive	Dead	AOR (95% CI)	p-value
1	Ventilation not required	47	2	0.48 (0.13-0.83)	0.009*
	Ventilation required	3	3		
2	No respiratory complaint	46	1	0.72 (0.83-0.33)	0.01*
	Presented with respiratory symptoms	4	4		
3	Normal RBS at admission	49	4	0.16 (-0.16-0.27)	0.60
	Hypoglycaemia at admission	1	1		
4	No abdominal complaint	40	1	0.12 (0.03-0.21)	0.01*
	Pain abdomen	10	4		
5	Normal abdominal examination	37	0	-0.04 (-0.09-0.08)	0.91
	Hepatomegaly present	13	5		
6	Normal liver function test	49	4	0.8 (0.41-0.93)	0.01*
	Deranged SGOT/PT	1	1		
7	Normal renal function test	47	4	-0.21 (-0.45-0.03)	0.08
	Deranged renal function	3	1		
8	Glassgow coma scale ≥9	49	4	-0.4 (-0.9-0.03)	0.07
	Glassgow coma scale <9	1	1		
9	No seizures at admission	48	3	0.31 (0.003-0.62)	0.04*
	Seizures at admission	2	2		
10	Normal platelets	23	0	0.05 (-0.03-0.13)	0.2
	Thrombocytopenia present	27	5		
11	Normal haemoglobin	13	0	0.007 (-0.08-0.09)	0.9
	Anaemia present (Hb <11)	37	5		
12	Haemodynamically stable	40	1	0.12 (-0.05-0.3)	0.17
	Hypotension at admission	10	4		
13	Fever ≤5 days before admission	42	2	0.09 (0.03-0.2)	0.05*
	Fever >5 days before admission	8	3		
14	Defervescence of fever <4 days of hospital stay	32	0	0.02 (-0.07-0.12)	0.6
	Defervescence of fever ≥4 days of hospital stay	18	5		

[Table/Fig-3]: Association of variables with mortality.

DISCUSSION

Scrub typhus is commonly found in Himachal Pradesh during the rainy season, the disease claims many lives each year, owing to a lack of awareness and sensitisation in peripheral health institutions [1]. Because no previous research had been conducted in the tribal region of state, particularly in the pediatric population, this study was designed to provide overview of scrub typhus among the pediatric and adolescent age groups.

Out of the 55 patients, 28 (50.9%) were males. There was no relationship between the sex distribution of the patients and the occurrence of the disease or its adverse outcome, which is consistent with Digra SK et al., retrospective analysis of the clinical profile of children suffering from scrub typhus in Jammu [7]. In the present study, majority 28 (50.9%) patients were in the age group of 7-12 years, followed by 16 (29.1%) in the age group of 1-6 years, only 11 (20%) patients belonged to the age group of 13-18 years. No significant relation was observed in the age distribution and occurrence of disease or mortality as was observed by Kumar BN et al., [8] and Chiranth SB et al., [9].

In the present study, cases of scrub typhus occurred in rainy season, started from the month of August till October, and no cases were seen thereafter, which is in direct relation to the extent of rainfall during this time of year. Bhopdhornangkul B et al.,[10], Kumar BN et al.,[8] and Sivarajan S et al., [11] also noted that vector distribution is more conductive in the rainy season.

Primary complaint observed among our patients were in form of fever (80%), vomiting (27.3%), pain abdomen (25.4%), respiratory (1.8%), rash (9%). Clinical features were fever (80%) and generalised lymphadenopathy (84%), followed by organomegaly (splenomegaly >hepatomegaly), anaemia (44%), hypotension (24%) with 9% presenting with shock, and neurological findings in 7%. Most authors noted fever as the presenting complaint in the patients [10,12-14].

Incidence of eschar in the present study (5.5%), was similar to various other Indian studies [1,7,15], but less compared to 20% in Kumar BN et al., [8] and 13% in Kumar M et al., [16]. In the study by Rose W et al., [17] eschars were present in 41% children with the following distribution: head, face and neck (20%); axillae (21%); chest and abdomen (12%); genitalia, inguinal region and buttocks (33%); back (4.5%); upper extremities (7%); and lower extremities (3%). The probable explanation for the low frequency of eschar in the present study patients may be due to variation in cutaneous immunity as well as dark skin of the patients. Clinical features from studies published on scrub typus from other states in India mentioned in [Table/Fig-4] [8,9,11,16,18].

Meningoencephalitis was observed in 4 (7.3%) patients in the present study similar to 6% observed by Kumar M et al., [16], which was lower than 22% in Sivarajan S et al., [11] 23 patients in Sharma S et al., [18], 28% in Kumar BN et al., [8] and 33% in study by Chirath SB et al., [9]. Many sicker patients would have been directly referred to higher medical facility, thereby explaining lower incidence in the present study.

In this observation study, the patients who presented with symptoms of cough, chest pain or shortness of breath were investigated with chest x-ray, among them nine patients had ARDS, which was associated with mortality (p-value <0.001). Gupta S et al., also observed ARDS among scrub typhus patients [19]. Similar incidence observed by Kumar BN et al., [8], and Sivarajan S et al.,[11]. A recent review also stated ARDS as one of the most life-threatening conditions

Parameters	Sharma S et al., (18)	Sivarajan S et al., [11]	Kumar BN et al., [8]	Chiranth SB et al., [9]	Kumar M et al., [16]	Present study
Age group (years)	19-68	18->60	8 m-18y	1-15	1-12	1-18
Place of study and year of publication	Meghalaya, India, 2015	Meghalaya, India, 2016	Dehradun, 2014	Bengaluru, Karnataka,2022	Puducherry, India, 2012	Chamba, Himachal Pradesh
Season during max cases	Not mentioned	Rainy	Rainy	Rainy	Rainy and Winter	Rainy

Clinical features	Myalgia (82.6%)	Fever (38.8%)	Fever (100%)	Fever (100%)	Fever (100%)	Fever (100%)
	Jaundice (26%)	Myalgia (62.2%)	Myalgia (14%)	Headache (44%)	Headache (11%)	Headache (18.9%)
	Breathlessness (30%)	Pain abdomen (67.7%)	Headache (18%)	Rash (26%)		Myalgia (10.9%)
	Cough (35%)	Headache (26.7%)		Altered sensorium (56%)	Myalgia (26%)	Pain abdomen (25.4%)
	Headache (91%)	Vomiting (23.3%)	Cough (35%)		Vomiting (49%)	Cough (16.4%)
	Nausea/vomiting (74%)	Cough (23.3%)	Vomiting (56%)	Hepatomegaly (74%)	Cough (51%)	Breathlessness (1.8%)
	Seizures (26%)	Hepatomegaly (26.7%)	Breathlessness (29%)	Hepatosplenomegaly (17%)	Pain abdomen (34%)	Rash (9%)
	Altered sensorium (61%)	Splenomegaly (24.4%)	Hepatomegaly (82%)	-	Breathlessness (37%)	Hepatomegaly (32.7%)
	Shock (22%)	Lymphadenopathy (22.2%)	Splenomegaly (59%)	-	Hepatomegaly (91%)	Splenomegaly (52.7%)
	Lymphadenopathy (13%)	Eschar (10%)	Eschar (20%)	-	Splenomegaly (60%)	Lymphadenopathy (83.6%)
	Splenomegaly (26%)	-	Lymphadenopathy (938%)	-	Lymphadenopathy (37%)	Eschar (5.5%)
	-	-	-	-	Eschar (11%)	-
Laboratory investigations	Raised ALP (61%)	Raised ALP (82%)	Raised serum creatinine (16.7%)	Raised ALT, AST (65%)	Raised ALT/AST (37%)	Raised ALT >40 IU/L (70.9%)
	Raised S Cr (30%)	Raised serum creatinine (14%)	Thrombocytopaenia <100000 (53%)	-	Raised serum creatinine (20%)	Raised AST >40 IU/L (56.4%)
	Jaundice (26%)	Jaundice (25%)	Raised ALP	-	Raised ALP (29%)	Raised serum creatinine (1.8%)
	WBC >11,000 (56%)	WBC >12,000 (25%)	ALT (51%)	-	WBC >11000 (37%)	Serum albumin <3 gm/dL (1.8%)
	Platelets <10×10^6/µL) (61%)	Thrombocytopaenia <100000 (20%)	-	-	Thrombocytopenia <100000 (31%)	WBC >11000 (30.9%)
	ALT >40 IU/L (39%)	AST >40 IU/L (100%)	-	-	Serum albumin <3 gm/dL (54%)	Chest X-ray abnormal (16.4%)
	AST >40 IU/L (26%)	ALT >40 IU/L (94%)	-	-	-	-
	Chest X-ray abnormal (13%)	-	-	-	-	-
Treatment	Doxycycline (100%)	Doxycycline (100%)	Doxycycline (69%) Chloramphenicol (31%)	Doxycycline (100%)	Doxycycline (100%)	Doxycycline (96.4%) Azithromycin (65.5%)
Death	None	5 (5.5%)	5 (7.5%)	1 (1.8%)	1 (2.9%)	5 (9.1%)

[Table/Fig-4]: Clinical presentation of scrub typhus from different parts of India [8,9,11,16,18].
WBC: White blood cell; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase

that can arise in scrub typhus patients, due to prolonged recruitment of inflammatory immune cells to the lung and vasculature damage. Patients with cough, septic shock, severe respiratory failure, and the need for intensive care with a lengthy ICU stay had radiographic abnormalities [20].

Doxycycline (34.5%), azithromycin (3.6%), and a combination of the two were used to treat the patients in 61.8 % of cases. Out of total 50% of those who received doxycycline alone became afebrile in 48 hours, another 26% in 96 hours, only 21% took longer than four days to defervescence. Five (14.7%) of those taking a combination of doxycycline and azithromycin became afebrile within 48 hours, 30% within 96 hours, 41% had fever even after four days, and 5 (14.7%) died. This group of patients was sicker, with a longer stay in the hospital, the requirement for mechanical ventilation, multiorgan symptoms associated with liver damage, a history of seizures, and a fever lasting more than four days before to admission. Doxycycline is an effective drug for scrub typhus and maximum patients benefitted from early start of treatment.

Total 8 (14.5%) patients required mechanical ventilatory support (average duration 19.5 hours). Subbalaxmi M et al., [21] from south India also had 10.4% patients admitted with diagnosis of scrub typhus and required ventilator support. The present study had 9% mortality among admitted patients, mainly those who had refractory shock at admission. Most studies had similar mortality due to shock, ARDS, multiorgan failure. Respiratory complaint and need for mechanical ventilation, pain abdomen with liver damage, history of seizures and duration of fever more than four days before presentation to hospital, defervescence of fever more than four days after admission were all associated with death. To reduce mortality, primary healthcare providers need to be more aware of scrub typhus suspicion and the importance of starting early doxycycline treatment in feverish children.

Limitation(s)

This was the first study to be conducted in a predominantly tribal hilly district in north India, with long winters from November to April. Because of faraway location of the hospital, that serves a tiny population, it's possible that population adjacent to neighbouring districts were visiting other hospitals for healthcare. As a result, the small number of patients in one year may not be indicative of the entire district.

CONCLUSION(S)

The present study observations includes a small number of patients and is limited to a local hospital with insufficient facilities to identify any co-existing diseases with scrub typhus. As a result of delayed referral and admission to the hospital, as well as delayed treatment commencement, the number of deaths and other complications may have increased. Scrub typhus in children is fairly common and should be included in the differential diagnosis of any acute undifferentiated febrile illness. Even if there is no eschar, a prolonged fever with non specific symptoms like myalgia and headache, rash, lymphadenopathy should alert the physician to investigate scrub typhus. Patients who access late treatment, present with shock,

liver damage, seizures, need mechanical ventilation, and multiple organ dysfunction syndrome have a higher mortality rate.

REFERENCES

[1] Mahajan SK, Rolain JM, Sankhyan N, Kaushal RK, Raoult D. Pediatric scrub typhus in Indian Himalayas. Indian J Pediatr. 2008;75(9):947-49.
[2] Kelly DJ, Fuerst PA, Ching W, Richards AL. Scrub typhus: The geographic distribution of phenotypic and genotypic variants of orientia tsutsugamushi. Clin Infect Dis. 2009;48(s3):S203-30.
[3] Soong L. Dysregulated Th1 immune and vascular responses in scrub typhus pathogenesis. J Immunol. 2018;200(4):1233-40.
[4] Bal M, Mohanta MP, Sahu S, Dwibedi B, Pati S, Ranjit M, et al. Profile of pediatric scrub typhus in Odisha, India. Indian Pediatr. 2019;56(4):304-06.
[5] Blacksell S, Kingston H, Tanganuchitcharnchai A, Phanichkrivalkosil M, Hossain M, Hossain A, et al. Diagnostic accuracy of the InBios scrub typhus detect™ ELISA for the detection of IgM antibodies in chittagong, bangladesh. Trop Med Infect Dis. 2018;3(3):95.
[6] Shimla [Internet]. [cited 2020 Jun 4]. Available from: https://mausam.imd.gov.in/shimla/.
[7] Digra SK, Saini GS, Singh V, Sharma SD, Kaul R. Scrub typhus in children: Jammu experience. JK Sci. 2010;12(2):95-97.
[8] Kumar BN, Dhar M, Mittal G, Shirazi N, Rawat A, Prakash KB, et al. Scrub typhus in children at a tertiary hospital in north India: Clinical profile and complications. Iran J Pediatr. 2014;24(4):387-92.
[9] Chiranth SB, Ashwini KR, Gowda VK, Sanjay KS, Ahmed M, Basavaraja GV, et al. Profile of neurological manifestations in children presenting with rickettsial disease. Indian Pediatr. 2022;59(3):222-25.
[10] Bhopdhornangkul B, Meeyai AC, Wongwit W, Limpanont Y, Iamsirithaworn S, Laosiritaworn Y, et al. Non-linear effect of different humidity types on scrub typhus occurrence in endemic provinces, Thailand. Heliyon. 202;7(2):e06095.
[11] Sivarajan S, Shivalli S, Bhuyan D, Mawlong M, Barman R. Clinical and paraclinical profile, and predictors of outcome in 90 cases of scrub typhus, Meghalaya, India. Infect Dis Poverty. 2016;5(1):91.
[12] Ghosh A, Dey PK, Hemram SK, Mukherjee M, Nair A. Clinical profile and predictors of therapeutic outcome with azithromycin in pediatric scrub typhus: A study from Eastern India. Trop Doct. 2022;004947552210815.
[13] Rathore DV, Imran DA, Pathania DM, Wani DG, Gupta DA. A study on clinico-laboratory parameters of children with scrub typhus in Garhwal region of Himalayan belt. Pediatr Rev Int J Pediatr Res. 2019;6(2):91-96.
[14] Rathi N, Kulkarni A, Yewale V. IAP guidelines on rickettsial diseases in children. Indian Pediatr. 2017;54(3):223-29.
[15] Bal M, Mohanta MP, Sahu S, Dwibedi B, Pati S, Ranjit M, et al. Profile of pediatric scrub typhus in odisha, India. Indian Pediatr. 2019;56(4):304-6.
[16] Kumar M, Krishnamurthy S, Delhikumar CG, Narayanan P, Biswal N, Srinivasan S, et al. Scrub typhus in children at a tertiary hospital in southern India: Clinical profile and complications. J Infect Public Health. 2012;5(1):82-88.
[17] Rose W, Rajan RJ, Punnen A, Ghosh U. Distribution of Eschar in pediatric scrub typhus. J Trop Pediatr. 2016;62(5):415-20.
[18] Sharma S, Masaraf H, Lynrah K, Lyngdoh M. Tsutsugamushi disease (scrub typhus) meningoencephalitis in north eastern India: A prospective study. Ann Med Health Sci Res. 2015;5(3):163.
[19] Gupta S, Bansal A, Biswal M, Williams V, Zaman K, Kumar A, et al. Clinical profile and predictors of intensive care unit admission in pediatric scrub typhus: A retrospective observational study from North India. Indian J Crit Care Med. 2020;24(6):445-50.
[20] Trent B, Fisher J, Soong L. Scrub typhus pathogenesis: Innate immune response and lung injury during orientia tsutsugamushi Infection. Front Microbiol. 2019;10:2065.
[21] Subbalaxmi M, Chandra N, Teja V, Lakshmi V, Rao M, Raju Y. Scrub typhus-experience from a South Indian tertiary care hospital. BMC Infect Dis. 2012;12(S1):77.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, Pt. Jawahar Lal Nehru Government Medical College, Chamba, Himachal Pradesh, India.
2. Associate Professor, Department of Paediatrics, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India.
3. Assistant Professor, Department of Medicine, Dr. Rajendra Prasad Government Medical College, Tanda, Kangra, Himachal Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mangla Sood,
Associate Professor, Department of Paediatrics, Indira Gandhi Medical College,
Shimla-171001, Himachal Pradesh, India.
E-mail: drmanglasood@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 16, 2022
- Manual Googling: May 12, 2022
- iThenticate Software: Jun 07, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 04, 2021**
Date of Peer Review: **May 14, 2022**
Date of Acceptance: **Jun 09, 2022**
Date of Publishing: **Aug 01, 2022**