

Clinical Profile, Complications and Outcome of Scrub Typhus in Children: A Hospital Based Observational Study in Anantapur

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1. Introduction

Scrub typhus, an important cause of tropical fever in northern Australia, the western Pacific islands and South Asia including India, is caused by a zoonotic obligate intracellular, gram negative bacteria, transmitted by a bite of trombiculid mite, the chigger [1, 2]. The disease is grossly under - diagnosed in low and middle income countries (LMICs) as the presentation and index of suspicion is low among clinicians. Limited awareness about the disease and lack of diagnostic facilities in developing nations like India are also important reasons for the under - diagnosis of the disease and delay in specific treatment have been reported to be associated with increased case fatality rates [2]. Scrub typhus in India was first ever reported in 1981 and a hospital based study carried out in 2004 found 28 cases of scrub typhus among 876 enrolled febrile patients [3]. Scrub typhus can manifest with nonspecific symptoms, such as fever, myalgia, hepatosplenomegaly, lymphadenopathy and thrombocytopenia and hence it should be considered as an important cause of acute undifferentiated fever in tropical and subtropical regions [5–7]. Although few studies have been reported previously, the data of scrub typhus in children is scarce. Therefore, a hospital based study was conducted in Anantapur district to study the clinical, laboratory profile and therapeutic outcome of scrub typhus in children aged 1–12 years of life.

2. Methods

Ethical approval

The study was approved by the Institute Ethical Committee (IEC) of Government Medical College, Anantapur, Andhra Pradesh, India. Written and oral consents were taken from the informants.

Hospital setting, patient selection and diagnosis

A prospective observational study was conducted at Anantapur Medical college, a tertiary care teaching hospital situated in Andhra Pradesh over a period of 12 months (1st Feb 2021 - 31st Jan 2022). Children aged 1–12 years were included in the study. All suspected cases with fever (n = 234) but without any identifiable infection along with presence of one or more of the following clinical features

(rashes, oedema, hepatosplenomegaly, lymphadenopathy and eschar) were subjected to serological test for scrub typhus. Common infectious conditions such as that could clinically mimic scrub typhus were ruled out by performing the following tests: peripheral smear and rapid antigen test for malaria, dengue (NS1 antigen and IgM antibody) test, urine and blood cultures as per clinical aspect. Leptospira serology and an HIV - ELISA were performed when clinically indicated. Cardiac evaluation (Echocardiography and CPK - MB) and cerebrospinal fluid (CSF) analysis was performed for selected cases with suspected myocarditis or meningoencephalitis respectively. Serological diagnosis for scrub typhus was made by IgM ELISA test. A favourable clinical response with oral doxycycline and azithromycin (defervescence within 48 hours) was considered as an additional evidence of the disease. Diagnosed cases (n = 57) were treated with a 7–10 day course of antibiotics [doxycycline 5–7 mg/kg/day twice daily and few were treated with doxycycline plus ceftriaxone (considering other co - infection) while those showing poor response with doxycycline (fever persisting even after 72 hours of therapy) and ceftriaxone were treated with oral or intravenous azithromycin for 5 days]. Chloramphenicol or rifampicin was not used in our centre for any patients. The response to treatment, the defervescence time, and the complications were noted. Children included in the study were followed up to discharge, mortality or leave against medical advice (LAMA).

Definitions

The following criteria were used to define the various complications in scrub typhus.

- **Acute Kidney Injury (AKI):** Rise of serum creatinine of at least 0.3 mg/dl or 50% higher than baseline within a 24–48 hour period or a reduction in urine output to 0.5 mL/kg per hour for longer than 6 hours.
- **Acute hepatitis:** Elevation of serum transaminases more than 2 times the normal upper limit.
- **Meningoencephalitis:** Altered sensorium along with signs of meningeal irritation and/or seizures associated with elevated protein and lymphocytic/neutrophilic cytology with normal or low sugar on CSF analysis.
- **Multiple Organ Dysfunction Syndrome (MODS):** Dysfunction of more than one organ, requiring intervention to maintain homeostasis.

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- **Myocarditis:** Child with tachypnoea, tachycardia and/or (S3 - gallop, shock) along with echocardiographic finding suggestive of reduced ejection fraction and elevated cardiac enzymes (CPK - MB).
- **Hyponatremia:** Serum sodium level less than 135 meq/L.
- **Hypoalbuminemia:** Serum albumin level less than 2.5 gm/dl.

Variables

Clinical data, including the duration of fever, associated symptoms, vital signs, and the general and systemic examination findings, were recorded. A careful search for eschar was performed in all patients. Data regarding age, sex and residential area were collected. Complete blood counts, chest X - rays, renal function test (urea, creatinine), liver function test (serum bilirubin, aspartate transaminase, alanine transaminase, serum albumin, total protein and phosphatase) and urinalysis were performed at the time of presentation for all cases and were repeated if necessary.

Statistical analysis

The data were analysed using SPSS software, version 16.0. Descriptive statistics in terms of frequency, percentage, mean and standard deviation were calculated.

3. Results

Clinical demographic profile of scrub typhus cases

Out of 234 cases tested for scrub typhus serology, 24.4% (n = 57) were diagnosed with scrub typhus with age ranging from 2 to 12 years with mean age of 8.8±3.8 years and 64.9% (n = 37) being male. Most (83.3%) of the children were diagnosed in between the months of September and November.

Table 1 shows the clinical demographic profile of children at the time of admission.

All children (n = 57) presented with fever. Among them, 43.4% (n = 25) had history of fever for less than 5 days and remaining 56.6% (n = 32), for more than 5 days. High grade fever (>101°F) was recorded in 85.9% (n = 49) children during admission. Other common symptoms were headache, myalgia, vomiting, nausea, abdominal pain, dry cough, shortness of breath, altered sensorium, maculopapular rashes and generalised tonic clonic seizures (GTCS) respectively. Important clinical signs noticed on examination included lymphadenopathy (60.5%), hepatomegaly (47.4%), edema (26.3%), jaundice (26.3%), splenomegaly (15.8%). A necrotic eschar which is considered as most useful diagnostic sign for scrub typhus was present in 11.8% (n = 6) children. Groin and axilla was the most common site for eschar seen in our study.

Table 1: Clinical demographic profile of scrub typhus

Clinical Manifestations	N	%	Demographic Data	N	%
fever	57	100	Age		
< 5 days	25	43.4	2 - 5 years	22	38.5
> 5 days	32	56.6	6 - 12 years	35	61.5
Headache	43	75	Sex		

Myalgias	39	68.4	Male	37	64.9
Vomiting	37	64.5	Female	20	35.1
Lymphadenopathy	35	60.5			
Nausea	34	59.2			
Pain abdomen	33	57.9			
Hepatomegaly	27	47.4			
Dry cough	20	35.5			
Oedema	15	26.3			
Jaundice	15	26.3			
Shortness of breath	13	22.4			
Splenomegaly	9	15.8			
Altered sensorium	8	14.5			
Rashes (maculopapular)	7	13.2			
Seizures (GTCS)	6	11.8			
Eschar	6	11.8			

Laboratory parameters of children with scrub typhus

Tables 2 depicts the laboratory findings of the children with scrub typhus. Out of 57 cases, 8 (14.5%) had platelet count between 50001 to 10000/mm³ and 13 (22.4%) had between 10000 to 50000/mm³. Eleven (19.7%) had direct bilirubin >2mg/dl and 34 (60.5%) had indirect bilirubin >1.2 mg/dl. Similarly, 17 (28.9%) had serum albumin >3.5gm/ dl and 28 (48.7%) had sodium level below 135 meq/l. Raised liver enzymes and raised creatinine values were seen in 34.2% and 65.8% respectively.

Table 2: Laboratory findings of children with scrub typhus

	N (57)	%
Raised bilirubin		
Direct (>2 mg/dL)	11	19.7%
Indirect (>1.2 mg/dL)	34	60.5%
Hypoalbuminemia (< 2.5 mg/dl)	40	71.1%
Hyponatremia (<135 meq/l)	28	48.7%
Raised liver enzymes (>45 IU/L)	20	34.2%
Raised creatinine (>1.5 mg/dl)	37	65.8%
Hematological parameters		
Platelet count (cells/mm ³)		
10000 - 50000	13	22.4%
50001 - 100000	8	14.5%
100001 - 150000	16	28.9%
150001 - 333000	20	34.2%

Complications of scrub typhus

Table 3 shows the most common complications were myocarditis (n = 41, 72.4%), hypoalbuminemia (n = 40, 71.1%), renal impairment (n = 38, 65.8%), hyponatremia (n = 28, 48.7%), hepatitis (n = 19, 34.2%) and severe thrombocytopenia (22.4%). Among 57 cases, 32 were managed in stepdown, 15 in general ward and 10 cases required pediatric intensive care unit (PICU) admission. Majority of children with myocarditis (S3 - gallop) received dobutamine (+/- low dose of diuretics) and those with shock received fluid boluses along with inotropes. Inotropes were given to 10 cases. Children with catecholamine resistant shock, worsening respiratory distress and Glasgow Coma Scale (GCS) less than 7 required ventilatory support. Out of 6 children who received ventilatory support, two of them expired due to multi - organ dysfunction syndrome. None of the children with AKI needed dialysis. Platelet transfusion was considered in all children with platelet count less than < 20, 000/mm³. Children with meningoencephalitis who showed increased CSF cell count (predominantly lymphocytic, few neutrophilic), raised protein and low sugar were treated as per protocol.

Table 3: Complications of scrub typhus

Characteristics	Frequency (N)	Percentage (%)
Cardiac dysfunction (myocarditis)	41	72.4%
Hypoalbuminemia	40	71.1%
Severe thrombocytopenia (<50000/mm ³)	13	22.4%
Acute kidney injury	38	65.8%
Hyponatremia	28	48.7%
Hepatitis	19	34.2%
MODS	2	3.5%

Doxycycline was commonly used (69.7%) in the treatment of scrub typhus followed by combination with azithromycin (18.4%). 51 (88.2%) recovered well and were discharged, 2 (3.9%) died due to multi - organ failure and 4 (7.9%) were discharged due to other reasons with lost to follow up (Table 4).

Table 4: Treatment and clinical outcomes of children with scrub typhus

Treatment	Frequency	Percentage
Antibiotics used		
Doxycycline only	40	69.7
Ceftriaxone and Azithromycin	2	3.9
Doxycycline and Azithromycin	10	18.4
Others	5	7.9
Clinical outcomes		
Recovered and Discharged	51	88.2
Death	2	3.9
Referred, LAMA	4	7.9

4. Discussion

The data of clinical laboratory profile as well as the outcome of scrub typhus in children in India is scarce. Males were more likely to be affected compared to females (64.5% versus 35.5%) [8–10]. The mean age of children in the present study was 8.8 years with two - third in between 6–12 years similar to findings reported by Bhat et al (2014) from north India [7]. The incidence of scrub typhus increased as the age increased in the present study which could be due to frequent exposures of chiggers in older children especially males while playing outdoor.

The clinical manifestations in scrub typhus are nonspecific and have wide variations in presentation. Majority of children in the present study were symptomatic (with fever, headache and myalgia). Recent studies conducted by Kumar et al and Palanivel et al also demonstrated fever to be present in all cases [7, 11]. Hepatomegaly was seen in in 47.4% whereas edema and jaundice were noticed in 26.3% each. Edema has been reported from 37% up to 60% in two studies from India [7, 11]. Lymphadenopathy in the present study was 60.5% which was almost similar to a study done in Srilanka by Silva et al [12] while Kumar et al found low incidence of lymphadenopathy in their study [13]. Eschar in the present study was 11.8%, similar to earlier studies from India [6, 14]. A recent study (2019) in India by Bal et al in 201 children with scrub typhus demonstrated the presence of eschar in 17.9% cases [15].

However, few studies have reported the presence of eschar in 50–80% cases of scrub typhus [8, 16, 17]. In contrary, some authors have reported scrub typhus cases even without

the presence of eschar. Presence of eschar in a child with fever, thrombocytopenia and renal impairment can be a useful clinical tool in excluding dengue infection in children with scrub typhus [2, 10, 18, 19].

Previous studies have observed rashes ranging from 15–91% but in our study, rashes were observed only in 13.2% of cases [8, 16–18, 20].

Myocarditis (72.4%), hypoalbuminemia (71.1%) and AKI (65.8%) were three major complications seen in children with scrub typhus in the present study. Majority of children with myocarditis had shock at presentation and required fluid, diuretic therapy, fluid restriction, boluses and inotropic support as required. None of the AKI cases required dialysis as they improved with conservative management. The reason for renal impairment in majority of cases with scrub typhus may be due to multi - organ involvement/failure whereas pre - renal cause due to intravascular fluid depletion could also be another reason for acute kidney injury. The comparison of complications in the present study with other previous studies have been depicted in Table 6. Although the proportion of complications in a study done by Kumar et al. was low than the present study, myocarditis (34%), hypoalbuminemia (54%) and AKI (20%) comprised three leading complications in their study [6]. Another recent longitudinal study (2016) in Meghalaya in 90 scrub typhus cases with mean age (SD) 36.3 (13.4) years showed that acute hepatitis (n = 15, 16.7%), pneumonitis (n = 14, 15.6%) and AKI (n = 11, 12.2%) were common complications with 38.5% (n = 5) death due to MODS. This suggests that the complication rate in children are much higher when compared to adults with scrub typhus [21].

A recent Cochrane review (2018) concluded that tetracycline, doxycycline, azithromycin, and rifampicin are effective drugs available for the treatment of scrub typhus and suggested that there may be little or no difference between tetracycline, doxycycline, and azithromycin as treatment options. The review also found that there were few treatment failures with the above mentioned drugs [22]. Majority of children in the present study were treated with doxycycline and showed a favourable clinical response. Previous studies have also shown a similar clinical response to doxycycline [8, 16, 18, 23]. Mortality rate in our study (3.9%) was lower than the study conducted by Kamarasu et al (15%) and Rathi et al (9%) [10, 24].

The present study has some limitations. As the study was conducted in a tertiary care referral hospital, the present findings may not reflect the exact burden of the disease in the community. Scrub typhus was diagnosed with IgM ELISA as indirect immunofluorescence test which is considered as the gold standard diagnostic test and is not easily available in many hospitals in India.

5. Conclusion

Scrub typhus should be considered as a differential in any community acquired undifferentiated febrile illness regardless of the presence of an eschar, and needs empirical therapy along with testing for scrub typhus. Myocarditis and acute kidney injury are important complications which when

addressed early can prevent mortality. Use of doxycycline shows a favourable outcome.

These authors contributed equally to this work

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