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Research Article

SCRUB TYPHUS – THE DANGER OF BEING UNDETECTED: LABORATORY INVESTIGATIONS AND CONTEMPORARY INFECTIONS

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ABSTRACT

Objectives: To identify scrub typhus cases among acute undifferentiated febrile illness (AUFI) by laboratory investigations. To determine the efficacy of immunoglobulin M-enzyme-linked immunosorbent assay (IgM-ELISA) in detecting the cases of scrub typhus and to compare the Weil–Felix test, rapid test, and IgM-ELISA for the diagnosis of scrub typhus.

Methods: A total of 110 AUFI cases participated (65 from rural, 16 from semi-urban, and 29 from urban setups; 33 farmers, 15 animal rearing workers, nine drivers, 19 laborers, and 34 other jobs). Blood was collected after due explanation and consent.

Results: The Weil–Felix test tested 22 samples as positive, whereas the rapid card test, IgM-ELISA, and polymerase chain reaction detected 15 samples as positive for infection. The sensitivity and specificity of the Weil–Felix test were 66.67% and 87.36%, respectively. The sensitivity and specificity of the rapid card test and IgM-ELISA were 100%. There were coinfections with *Leptospira*, typhoid, and COVID-19.

Conclusion: Laboratory investigations revealed the various organ systems the disease could affect and that it could serve to determine the prognosis. The use of rapid card tests is on par with IgM-ELISA, making it a suitable candidate for diagnosing in remote setups.

Keywords: Scrub typhus, Acute undifferentiated febrile illness, Immunoglobulin M enzyme-linked immunosorbent assay, Rapid card test.

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INTRODUCTION

Scrub Typhus, being one of the most neglected diseases, is on the rise in the Indian subcontinent. At present, all 29 states and four out of the seven union territories are reporting outbreaks of scrub typhus spanning areas not only under military presence but also civil populations [1]. Rarely manifested with its typical triad of maculopapular rash, regional lymphadenopathy, and eschar, it may prove fatal if not correctly diagnosed and intervened.

Late diagnosis and delayed initiation of treatment remain the main reasons for the fatalities. Progression of severe scrub typhus may lead to acute respiratory distress, acute renal failure, meningoencephalitis, gastrointestinal bleeding, hypotensive shock, and coagulopathy [2]. In India, the case fatality rate varies from 1.3% to 33.5%, depending on the organ involvement [3].

Several tests are available with their own benefits and limitations. The Weil–Felix test, being cheaper, is still used despite lower specificity and sensitivity. Immunoglobulin M-enzyme-linked immunosorbent assay (IgM-ELISA) has been evaluated and found to be satisfactory in diagnosis. Rapid test (immunochromatography) is economical, and immunoglobulin G (IgG) and IgM antibodies can be detected simultaneously. Indirect immunofluorescent assay and indirect immunoperoxidase are considered the gold standard but are not available in a majority of health setups. This study was carried out to analyze the various laboratory investigation results, and to see if rapid card tests could be used as a diagnostic tool for the benefit of remote areas.

MATERIALS AND METHODS

Setting of the study
The study was conducted in a tertiary care teaching hospital, including all cases presenting with acute undifferentiated febrile illness (AUFI).

Study population
Cases include both outpatients and inpatients. The study duration was between September and October 2022.

Sample size
A total of 110 samples from pediatric and adult cases presenting with AUFI were obtained in the given period.

Type of study
Cross-sectional analytical study.

Inclusion criteria
All patients presenting with AUFI due to infectious etiology.

Exclusion criteria
Patients presenting with fever due to metabolic causes or other non-infectious etiology.

Procurement of permission
The purpose of the study was explained to the patients presenting with fever, and written informed consent was obtained before enrolling in the study. Institutional ethics clearance was obtained duly before starting the study.

Methods
Due consent was obtained in a written format. For evaluating AUFI, 3–5 mL of blood was collected in two separate containers. The first one was used for complete blood count, peripheral smear, and smear for malarial parasites and microfilaria. The second container, serum, was separated from the blood, and investigations such as C-reactive protein (CRP), anti-streptolysin O titer, WIDAL, dengue, chikungunya, and leptospiral serology were tested.

Table 1 : Risk factors

Risk factor	No. of AUFI cases (%)	No. of scrub typhus-positive cases	No. of scrub typhus-negative cases	Value (as per Chi-square)	p-value
Travel history	18 (16.36)	2	13	0.060	0.807
Insects bite	32 (29.09)	9	6	8.044	0.005*
Rearing of animal	18 (16.36)	4	11	7.719	0.005*
Open defecation	16 (14.55)	5	10	0.034	0.853
Rat infestation	23 (20.91)	7	7	0.656	0.418

*p≤0.005. AUFI: Acute undifferentiated febrile illness

Table 2: Signs seen in scrub typhus-positive cases

Clinical signs in scrub typhus patients	No. of cases (%)	p-value
Pallor	2 (13.33)	<0.001*
Icterus	0	-
Eschar	0	-
Rashes	4 (26.66)	0.002*
Lymphadenopathy	3 (20)	0.600
Hepatosplenomegaly	1 (6.66)	<0.001*
Pedal edema	0	-

*p≤0.005; figure in parenthesis denotes the percentage of scrub typhus cases

Table 3: Symptoms seen in cases of scrub typhus

Clinical manifestation in scrub typhus patients	No. of cases (%)
Fever	15 (100)
Headache	7 (46.66)
Cold	4 (26.66)
Cough	5 (33.33)
Eye complaints	1 (6.66)
Loose stools	2 (13.33)
Myalgia	3 (20)
Joint pain	5 (33.33)
Nausea and vomiting	2 (13.33)
Body ache	5 (33.33)
Breathlessness	1 (6.66)
Loss of weight	1 (6.66)
Chest pain	2 (13.33)
Loss of appetite	3 (20)
Urinary complaints	2 (13.33)
Easy fatiguability	1 (6.66)

Figure in parenthesis denotes the percentage of scrub typhus cases

Table 4: Laboratory investigations in scrub typhus patients

Laboratory investigation in scrub typhus patients	No. of patients (%)
Leukocytosis (WBC >11,000 cells/cu.mm)	9 (60)
Thrombocytopenia (platelets <1.5 Lakhs cells/cu.mm)	4 (26.66)
Anemia (Hb in males <13 g%, females<11 g%)	6 (40)
SGOT elevated (normal 12–38 IU)	11 (73.33)
SGPT elevated (normal 7–41 IU)	10 (66.66)
ALP elevated (normal 53–128 IU)	7 (46.66)
GGT elevated (normal<55 IU)	8 (53.33)
Protein levels (normal 6.7–8.6 g/dL)	11 (73.33)
Bilirubin elevated (normal 0.3–1.3 mg/dL)	6 (40)
Urea (normal 15–40 mg/dL)	9 (60)
Creatinine (Normal 0.6–1.2 mg/dL)	7 (46.66)

WBC: White blood cell, Hb: Hemoglobin, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Chemicals and reagents

After performing all these investigations, the second serum container samples were tested for Weil–Felix reaction, scrub typhus IgM-ELISA, and a rapid card test. Antigens for Weil–Felix reaction were obtained from the King Institute of Preventive Medicine and Research, Guindy. A single titer of ≥1:160 or a four-fold rise in titer from two consecutive samples submitted a week apart is considered significant.

Diagnostic kits

For IgM-ELISA, commercial ELISA kits (Panbio Ltd, Brisbane, Australia) were used. A tsutsugamushi rapid qualitative card test, by J. Mitra & Co. for the detection of IgG and IgM was used. The cases which are found to be positive for scrub typhus were noted. Any coinfections or relevant findings were noted.

Table 5: Serology and peripheral smear for the study population

Serology and peripheral smear	No. of cases (%)
CRP	21 (19.09)
ASO	8 (7.27)
Typhoid (widal test)	20 (18.18)
Dengue (NS1 antigen detection)	10 (9.09)
Malaria (peripheral smear)	1 (0.91)
Chikungunya (IgM capture ELISA)	0
Scrub typhus (PCR)	15 (13.63)
Leptospirosis (MAT)	1 (0.91)
Covid-19 (RT-PCR)	2 (1.81)
Etiology not identified*	36 (32.73)
Total	114

*May be due to febrile gastroenteritis, acute viral fever, viral pneumonia, HIV, Hemophilus influenza pneumonia, tuberculosis, UTI: Urinary tract infection, CRP: C-reactive protein, ASO: Anti-streptolysin O, IgM: immunoglobulin M, ELISA: Enzyme-linked immunosorbent assay, PCR: polymerase chain reaction, MAT: Microscopic agglutination test, RT-PCR: Reverse transcription polymerase chain reaction

Table 6: Coinfections seen in scrub typhus

Coinfection/concomitant rise	No. of cases of scrub typhus (%)
CRP	1 (6.66)
Typhoid	1 (6.66)
Dengue	0
Malaria	0
Chikungunya	0
Leptospirosis	1 (6.66)
COVID-19	1 (6.66)

CRP: C-reactive protein

Table 7: Efficacy of Weil–Felix test, rapid card test, IgM-ELISA

Tests performed	No. of cases positive for the test	No. of cases negative for the test	Sensitivity (%)	Specificity (%)
Weil–Felix test	22	88	66.67	87.36
Rapid card test	15	95	100	100
IgM-ELISA	15	95	100	100

IgM-ELISA: Immunoglobulin M-enzyme-linked immunosorbent assay

OBSERVATION AND RESULTS

A total of 110 AUFI cases were included in the study after getting written consent to participate in the study from the patient. Their blood was withdrawn, and laboratory investigations were performed, as mentioned above.

DISCUSSION

Scrub typhus presents mostly as a vague case of fever without the typical triad of maculopapular rashes, regional lymphadenopathy, and eschar. The symptoms often mimic other tropical diseases, which might prolong the time for proper diagnosis. The importance of laboratory work with respect to the disease can be seen in three main aspects.

First, the results would be helpful in identifying which organ is under stress due to the disease. Reduced white blood cell count, thrombocytopenia, raised serum creatinine, and raised liver enzymes are seen in a majority of the patients. Disseminated intravascular coagulation and hemophagocytic syndrome [4] are some of the serious consequences of infection. Hepatic failure, jaundice, ascites, acute renal injury, tubular necrosis, and pigmented nephropathy are other uncommon yet serious outcomes that further help to reduce morbidity and mortality.

Second, the testing process for the disease is nowadays simplified by the newer advent of devices such as IgM-ELISA, polymerase chain reaction (PCR), and rapid flow assay. The benefit of these methods, coupled with mass screening programs will help in early identification and treatment.

Third, coinfections are pretty common with scrub typhus. The disease itself has a vague presentation similar to the common diseases encountered.

Of the 110 cases, 15 (13.6%) tested positive for scrub typhus in the card test and IgM-ELISA. The prevalence of scrub typhus varies from 0 to 8% to 60% in different countries [5]. Scrub typhus was diagnosed by Weil–Felix, card test, and IgM-ELISA. The sensitivity and specificity of the Weil–Felix test were 66.7% and 87.4%, respectively, whereas the sensitivity and specificity of the card test and ELISA were 100% (Table 7). An earlier study conducted in Thailand using SD Bioline ICT had reported sensitivity and specificity to be 66.7% and 98.4%, respectively [6]. On the contrary, Lee *et al*. reported higher sensitivity (72.6%) of SD Bioline ICT in the Korean population [7]. Another ICT, ImmuneMed rapid diagnostic test (RDT), was found to be more sensitive (98.6%) than SD Bioline RDT (84.8%) in the Korean population [8]. In a study by Prakash *et al.*, the sensitivity of 44% and 87% were observed with the Weil–Felix test and IgM-ELISA, respectively [9]. Thus, rapid card tests could be made available for screening purposes in subcenters and primary health center levels for early diagnosis and prevention of complications [10,11]. This could be done in endemic regions, whereas tertiary centers could be armed with confirmatory testing apparatuses such as PCR, Institute of Public Accountants, or Institute of Financial Accountants. Still, the test could not be completely considered a diagnostic tool, as per the Department of Health Research–Indian Council of Medical Research (ICMR) guidelines [12].

Of 15 positive cases, nine samples (60%) had leukocytosis. Leukocytosis and thrombocytopenia are two common features (Table 4) seen in complete blood count (CBC) [13]. A significant proportion of cases had elevated serum glutamic-oxaloacetic transaminase (11 samples/73.33%), serum glutamic-pyruvic transaminase (10 samples/66.66%), and 11 (73.33%) had reduced blood protein level, indicating hepatic involvement, whereas nine samples (60%) had raised urea, pointing to renal involvement. Six samples (40%) had anemia, whereas four (26.66%) had thrombocytopenia. Moreover, physical manifestation was not prominent, with only two cases (13.33%) having pallor and none Jaundiced (Table 2). Surprisingly, one case had hepatosplenomegaly, and three were found to have lymphadenopathy. One case (6.66%) had raised CRP (Table 5). Previous studies revealed that abnormalities of liver function test are common in children with scrub typhus. Increased aspartate aminotransferase (AST) levels may help as a clue for the diagnosis of scrub typhus in endemic areas where rapid laboratory tests are not available. The severity of the disease is associated with elevated AST, alanine aminotransferase, and hypoalbuminemia [14].

Of the scrub typhus-positive cases, 6.66% cases were co-infected with either *Leptospira*, COVID-19, or typhoid (Table 6). A study done in Odisha [15] supported the fact that 36.2% of cases were positive for malaria, dengue, or chikungunya. Similarly, a study done in Arunachal Pradesh [16] confirms the coinfection rate of scrub typhus and leptospirosis as 25%. This may be due to greater exposure to mites/mammals in the field and to rodents during household activities at home. This also highlights the fact that *Orientia tsutsugamushi* is capable of not even sparing any patient, even concomitant COVID-19 infection. There was an interesting finding that one of the tested cases was both scrub typhus and *Leptospira* positive. A CBC test revealed the patient had acute myeloid leukemia. Immunocompromised patients are susceptible to multiple infections, as in this case.

The pathophysiology of liver and renal complications involves the organism invading the hepatic and renal parenchyma [17], liberating markers specific to the organ and leading to damage. In India, the case fatality rate varies from 1.3% to 33.5%, depending on the organ involvement [3]. Complications such as meningoencephalitis, acute respiratory distress syndrome (ARDS), sepsis and septic shock, perivasculitis in the brain and lungs, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome are the leading cause of fatalities in complicated cases. Poor prognostic factors include ARDS, septic shock and the necessity for intensive care unit admission, poor APACHE II scores, and pregnancy [18]. Furthermore, as of 2017, Only five countries have established scrub typhus surveillance systems – China, Taiwan, South Korea, Japan, and Thailand [19]. Therefore, early diagnosis by wider screening serves as an important basis for complete control over the disease.

Finally, one must not underestimate the role of gaining proper history and examination from the patients. On analyzing by Chi-square technique, we found that there is a significant relation between acquiring infection and contact with animals and a history of a vector bite (Table 1). The vast majority of those who did not use toilets reported defecating in fields [20], and the individuals who reported defecating in the bushes are at risk of getting infected. Moreover, there was no calculated significant relation with any travel history, open defecation, or rat infestation. This may be attributed to two reasons: Patients' hesitancy about revealing their environmental condition or the improvement of housing and toilet facilities due to various programs and community outreach.

The most common clinical presentations in this study were fever, myalgia, headache, body ache, cough, cold, nausea, abdominal pain, vomiting, breathlessness, and diarrhea (Table 3). Similar clinical presentations were observed in Korean patients and also in various studies conducted in India [21,22].

Eschar at the site of bite of the larval mite/chigger is highly indicative of scrub typhus infection but is seen in varying proportions in different studies. In the current study, eschar was not noted in any of the 110 cases. Vivekanandan *et al*. [23] (46%), Chrispal *et al*. [24] (45.5%), and studies from Vietnam [25,26], Taiwan [27], and Korea [28,29] reported slightly higher incidences of eschar probably due to fair-skinned population of these studies, which increases the chances of finding eschar. Premaratna *et al*. [30] also postulated that small/early eschar might be easily overlooked in dark-toned patients.

Some abnormal symptoms such as chest pain, ocular complaints, and loss of weight were also noted, which might denote progression toward complications. The clinical manifestations vary from minimal or common symptoms to severe fatal illness with multi-organ

dysfunction. The abnormalities in cell counts and liver and renal functions in the present study were consistent with those reported in other studies [30,31].

CONCLUSION

Scrub typhus could be suspected clinically, but a complete picture could only be obtained with a proper laboratory workout. Significant clinical features and relevant history could help us to narrow our differential. The majority of patients had involvement of the liver, followed by kidney and lymph nodes. Some also had anemia and thrombocytopenia. This indicates the need for serious detection and clinical monitoring of scrub typhus-positive patients. It was found that for testing, the Weil–Felix test was found not reliable, whereas the rapid card test was equally good compared to IgM-ELISA. This is a simple test easily performable by the village health workers and could be deployed in rural areas for routine and early diagnosis in endemic areas. Coinfections with *Salmonella*, *Leptospira,* dengue, COVID-19, etc., diseases which have similar presentations, such as scrub typhus, complicate the diagnosis and treatment aspect, where the rickettsial disease may go unnoticed. Furthermore, the presence of malignancy may complicate the management, as it might predispose to an aberrantly functioning immune system.

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AUTHOR'S CONTRIBUTION

The contribution from each author is equal.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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