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Prognostic Profile of Scrub Typhus in Association with Co Existing Clinical Infection in Hadoti Region of Rajasthan

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Abstract

Scrub typhus is a disease caused due to infection with *Orientia tsutsugamushi*, and is spread by *leptotrombidium* mites (chiggers). In tropical areas, ***concurrent infection*** of ***malaria*** and ***dengue*** can occur as both are transmitted by mosquito. But the mode of transmission of ***scrub typhus*** is exclusive in terms of a vector insect, a bite by chigger larvae, and therefore has no connection with other mosquito-borne or air-borne or water-borne infections. Henceforth concomitant O.tsutsugamushi with other parasite or chronic infection in an individual is infrequent.

We retrospectively studied clinically suspected and serologically confirmed cases of ***scrub typhus*** presented at medicine department of tertiary health care hospital at Kota. The cases were divided into two groups: 1. Group A - Comprising of patients diagnosed with ***scrub typhus*** only and 2. Group B- Patients diagnosed with ***scrub typhus*** and any other parasitic (***malaria***), viral (***dengue***, HBS, HSV) or other bacterial (tuberculosis) infection. The clinical data and outcome of the two groups were compared and statistically analyzed.

A total of 37 ***scrub typhus*** cases were included and during the study, concomitant another infection was noted among 18 (48.65%) of cases. These were ***Dengue*** *virus* (27.03%), *Plasmodium vivax* (18.92%), *Plasmodium falciparum* (8.11%), *Mycobacterium tuberculosis* (2.70%), *Herpes simp*lex virus (2.70%) and *Hepatitis B virus* (2.70%).

In this study, the most common complications included thrombocytopenia (75.68%), anaemia (48.65%), urinary tract infection (45.95%), abnormal respiratory system findings (40.54%), encephalitis (27.03%) and splenomegaly (24.32%). The comparison of groups showed that patients with coinfection presented with more severe deranged laboratory reports; severe complications involving CNS, respiratory system and the urinary system.

Thus, concomitant infection in a patient of scrub typhus is not infrequent and treating physicians should keep this in mind while making a diagnosis,hence ones a diagnosis of scrub typhus has been made,relevant concomitant intection like dengue,malaria etc should also be taken into account as they influence the prognosis gravely.

Keywords: Concurrent Infection, Dengue, Scrub Typhus, Malaria.

Introduction

Scrub typhus, previously known as Rickettsia Orientalis (or R. tsutsugamushi) is conveyed by *leptotrombidium* mites (chiggers) and has a wide rodent reservoir .The mode of transmission to humans is the bite of the larva of these infected chiggers.

Further transmission of infection among humans is not seen, as the infection does not spread directly from man to man or through the medium of his common ectoparasites. The incubation period is 6-18 days, followed by the onset of symptoms including fever , headache, cough, swollen eyelids and face, rash on the torso, painful draining lymph nodes or general lymphatic glandular enlargement. The examination may reveal the development of eschar at the site of the infection; multiple eschars can occur at the trunk. Other symptoms may include nausea, vomiting, tinnitus and epistaxis. The transient rash appears between the fifth and eighth days of the disease and occurs mainly on arms, thighs, and trunk.

The severity of disease presents as organ dysfunction that may include respiratory, renal, or hepatic dysfunction; shock; meningoencephalitis; DIC; delirium; papilloedema; and coma.[1]. The mortality rate varies from 1% to 35% and is particularly higher in untreated cases.[2]

Dengue fever is caused by dengue virus (flaviviruses) and spread by the bite of a mosquito (mainly *Aedes aegypti, A. albopictus).* Incubation period averages 4-7 days with the onset of fever, headache, retroorbital pain, myalgia. It is a fast-spreading outbreak-prone arboviral disease and has become one of the major public health concerns in the country. During 2016, a total of 1,29,166 cases and 245 deaths were reported.[3]

Malaria is a protozoan (genus *Plasmodium*) infection and transmitted by the bite of infected *Anopheles* mosquitoes. Initial symptoms include fever, headache, fatigue, abdominal discomfort and myalgia. The malaria cases have consistently declined from 1.87 million to 0.49 million from 2003 to 2017 (till July). Though this shows that the incidence of malaria is decreasing in India but still it is a common parasitic organism affecting the health of people.[3]

In tropical areas, concurrent infection of malaria and dengue can occur as both are transmitted by mosquito. But the mode of transmission of scrub typhus is exclusive in terms a vector insect, a bite by chigger larvae, and therefore has no connection with other mosquito-borne or air-borne or water-borne infections. Henceforth concomitant *O. tsutsugamushi* with other parasite or chronic infection in an individual is not common . But during this study, we have come across a variety of mixed infection in scrub typhus patients. This was certainly an eye-opener and now there is a need to understand the overall pathological effect/progress of the concomitant infection. Undermining a concurrent parasitic infection during diagnosis may lead to wastage of time and may compromise the health of a patient. This can happen during the reemergence/ outbreaks of dengue and malaria in India, clinicians might undermine cases of scrub typhus due to low awareness of the infection.

Materials and Methods

We prospectively studied clinically suspected and serologically confirmed cases of scrub typhus who presented to tertiary health care hospital at Kota. Demographic data, detailed history, was noted; thorough clinical examination and investigations were performed. Most of these patients presented as an acute febrile illness. Initially, all previous medications were stopped to exclude drug fever.

The investigations performed were complete blood count, ESR and CRP, hemoglobin, platelet count, leukocyte

count and differential, electrolytes, fasting blood sugar, creatinine, urea, alkaline phosphatase, AST, ALT, LDH, creatine kinase, Liver function tests, urinalysis, chest x-ray, blood and urine cultures, abdominal ultrasonography, sputum and tuberculin skin test. Laboratory investigations used for scrub typhus detection was IgM ELISA System; for dengue by NS1 antigen and/or IgM serodetection; for Plasmodiumfalciparum and Plasmodium vivax malaria by card test and for swine flu by H1N1 serodetection. CT scan of thorax and abdomen, the brain was done wherever required.

The cases were divided into two groups: 1. Group A - Comprising of patients diagnosed with scrub typhus only and 2. Group B- Patients diagnosed with scrub typhus and any other parasitic (malaria), viral (dengue, HBS, HSV) or other bacterial (tuberculosis) infection. The clinical data and outcome of the two groups were compared and statistically analyzed. Laboratory reports and clinical data, of the two groups, were compared using the independent t-test. Statistical significance was set at $p < 0.05$.

A total of thirty-seven (37) serologically confirmed cases of scrub typhus were included in this study.These patients were thoroughly clinically examined and investigated. Patients were of Kota, Bundi, Barah, Jhalawar, tonk and dosa district of Rajasthan.

The previous history of relevant medical condition noted was hypertension (2 cases), neurofibromatosis (1), CVA (1), IHD (1), COPD (1), Hiatal Hernia (1), Cholelithiasis (1), recent obstetric history- one female was 6 months pregnant and another female was post-partum 9 days.

Table 1: Baseline characteristics, and signs and symptoms, observed in the cohort are given in.

Parameter	Number	Percentage (%)
Age		
<20	1	2.70
20-50	28	75.68
>50	8	21.62
Sex		
Male	20	54.05
Female	17	45.95

Among these 37 cases, 20 (54%) were male and 17 (46%) were female. Patients ranged from 16 to 77 years with a mean age of 38.46 ± 14.77 years.

Table 2: Signs & symptoms of all patients in this study (n=37)

Symptoms	No	Percentage
Fever	33	89.19%
Breathlessness	9	24.32%
Cough	8	21.62%
Diarrhea	3	8.10%
Nausea	3	8.10%
Weakness	10	27.02%
Altered sensorium	9	24.32%
GTCS	5	13.51%
Body ache	4	10.81%
Increased urine frequency	1	2.70%
Icterus	1	2.70%
Vomiting	2	5.40%
Anasarca	2	5.40%
Dyspnea	5	13.51%
Chills	2	5.40%
Headache	1	2.70%

Signs	No	Percentage
Eschar	06	16.21%
Rash	13	35.10%
Icterus	3	8.10%
Pallor	2	5.40%
lymphadenopathy	2	5.40%
Hepatomegaly	6	16.22%
Splenomegaly	9	24.32%

A most common complaint with which these cases presented was fever (89.19%) followed by altered sensorium (24.32%), cough (13.51%), breathlessness (8.51%), weakness (8.51%) and diarrhoea (8.51%).

Table 3: Laboratory confirmed diagnosis of patients

Infection detected	**Incidence (n)**	**Percentage (%)**
Orientia tsutsugamushi (ST)	37	100
Dengue virus(DV)	10	27.03
Plasmodium vivax (PV)	7	18.92
Plasmodium falciparum (PF)	3	8.10
Mycobacterium tuberculosis (TB)	1	2.70
Hepatitis B virus (HBS)	1	2.70
*Herpes simp*lex virus (HSV)	1	2.70
Combinations		
ST only	19	51.35
ST+DV	6	16.22
ST+PV	4	10.81
ST+PF	1	2.70
ST+HSV	1	2.70
ST+TB	1	2.70
ST+DV+PV	2	5.40
ST+DV+PF	1	2.70
ST+DV+HBS	1	2.70
ST+PV+PF	1	2.70
Total cases with mixed infection	18	48.65

A total of 9 combinations occurred in this series as shown in table no 3. Double infection was noted among 13 (35.16%) and triple infection in (13.51%) respectively. Most common double combination was ST +DV (n=6, 16.21%), followed by ST + PV (n=4, 10.81%). Most common triple infection noted was ST+ DV+PV (n=2, 5.40%).

Table 4: Laboratory findings in all cases

Investigation	**Mean±SD**
Systolic blood pressure	111.31±27.72
Diastolic blood pressure	73.70±13.05
Platelets	80777.78±75020.43
Hb	10.41±2.5
TLC	9171.667±6060.07
Urea	99.81±83.26
Creatinine	1.85±1.38
Bilirubin	5.39±6.52
SGOT	202.84±145.2
SGPT	103.43±66.59
LDH	1763.36±1341.08
PT	21.38±9.72
INR	1.97±1.17

Table 5: Complications noted in the cohort (n=37)

Complications	Number	Percentage
Thrombocytopenia	28	75.68
Shock	6	16.22
Hypotension	5	13.51
Anaemia	18	48.65
Leucopenia	4	10.81

Leucocytosis	5	13.51
Granulomatous lymphadenitis	2	5.40
DIC	1	2.70
CNS		
Meningoencephalitis	9	24.32
ADEM (Acute disseminated encephalomyelitis)	1	2.70
Deranged CSF report	4	10.81
GTCS	4	10.81
Respiratory		
Occasional crackles	3	8.10
Crepts in infra axillary area	3	8.10
Air entry decreased on the right side	1	2.70
b/l effusion	9	24.32
b/l effusion with prominent hilar nodes	1	2.70
effusion with consolidation (k-chest)	1	2.70
b/l heter opacities	1	2.70
b/ l haziness	2	5.40
ARDS	1	2.70
Abnormal Sputum report	1	2.70
Abdomen		
Splenomegaly	9	24.32
Hepatomegaly	6	16.22
Oedamatous GallBladder	8	21.62
Ascites	5	13.51
Grade 1 RMD	3	8.10
Grade 2 RMD	3	8.10
PID	1	2.70
Other		
Urinary tract infection	17	45.95
ARF	4	10.81
MODS	5	13.51
Assisted ventilation	4	10.81

The most common clinically relevant finding included thrombocytopenia (75.68%), anaemia (48.65%), urinary tract infection (45.95%), abnormal respiratory system findings (40.54%), encephalitis (27.03%) and splenomegaly (24.32%).

Table 6: Comparison of laboratory findings in the two groups

Parameter	Scrub typhus only (n=19) Group A	Scrub typhus + other infection (n=18) Group B	Significant difference
Platelets	80777.78± 75020.43	67687.5±51061.68	No
Hb	10.52±2.14	10.28571±2.93	No
TLC	6612.5±2487	12096.43±7583.8	**Yes**
Urea	71.64±69.61	130.15±88.57	No
Creatinine	1.34±1.04	2.4±1.52	**Yes**
Bilirubin	3.18±3.36	7.6±8.18	No
SGOT	236.9±168.69	179±130.3	No
SGPT	103.6±48.23	103.33±77.74	No
LDH	1473.25±882.02	2053.5±1698.11	No
PT	23.82±13.08	18.46±1.6	No
INR	2.18±1.56	1.71±0.47	No

Table no 5 shows that mean ±SD findings of laboratory investigations are more deranged in the with coinfection (mixed infection) but statistical significance was noted for TLC and Creatinine only. In with coinfection group, it was observed that severe complications and poor outcome

were more frequent than without coinfection. All the case fatalities in this cohort (5cases, 13.51%) belonged to group of coinfection as well as severe complications including abnormal Central Nervous System, urinary system and respiratory system findings were more frequent in this group compared to the other . Although , in Group A thrombocytopenia showed slightly higher incidence but the severity was more in Group B. (Table-6)

Table 7: Comparison of complications in the two groups

Complications	Without coinfection	With coinfection
Thrombocytopenia	16	13
Encephalitis	3	6
ADEM	1	0
GTCS	1	3
Deranged CSF report	1	3
Hypotension	2	2
Shock	1	5
Urinary tract infection	7	10
ARF	1	3
Positive chest X-ray	7	7
Abnormal auscultatory chest findings	2	5
ARDS	1	0
Splenomegaly	3	6
Hepatomegaly	3	3
Granulomatous lymphadenitis	2	0
MODS	1	4
OEDEMATOUS GB	3	5
ASCITES	3	2
GRADE 1 RMD	1	2
GRADE 2 RMD	2	1
PID	0	1
Assisted ventilation-intubated	1	3
Death	None	5

Result and Discussion

Although Scrub typhus has been reported from various parts of India, including Rajasthan, it is still an under-diagnosed disease.[4] previously most of the scrub typhus patients were reported from rural areas of India but nowadays it is seen in urban areas also.

There are few reports of **concurrent** malaria and dengue in a patient.[5,6,7,8] The important question that whether the impact of concomitant infection is more than individual infection has been addressed by a French study; where they showed that concurrent dengue and malaria does tend to be more severe in terms of thrombocytopenia and anaemia.[9.10] But there was no study reported in literature about the combined impact/pathology of coexistent scrub typhus with other infections.

A total of 37 scrub typhus cases were included and during the study, concomitant another infection was noted among 18 (48.65%) of cases. These were *Dengue virus* (27.03%), *Plasmodium vivax* (18.92%), *Plasmodium falciparum* (8.11%), *Mycobacterium tuberculosis* (2.70%), *Herpes simp*lex virus (2.70%) and *Hepatitis B virus* (2.70%).

In this study, the cohort comprised of 10 dengue patients and case fatality during in-hospital stay occurred in 3 cases (30%). And among these 3 case fatalities, two cases had infection with *P. vivax* as well. Thus, the case fatality in dengue cases is higher than other reports from this region; it implies that concomitant infection of scrub typhus/plasmodium has an additive pathological impact on the patient.

In our study total malaria cases in the cohort was 9 (24.32%), *P.vivax* was the predominate type detected in 6 cases (66.67%) followed by *P. falciparum* in 2 (22.22%) and one case (11.11%) had mixed infection (pv+pf)

respectively. Similar pattern was reported by Trupti[11] (pv-64.48%, pf-25.75%, mixed- 9.76%), and Muddiah[12] (pv-52.54%, pf-33.75%, mixed- 13.69%). Case fatality in malaria patients occurred in 2 cases (22.22%) and both were infected with *P. vivax.* Both of these cases were females; anaemic; platelet was below 21000; lab reports showed urinary tract infection; and were subsequently intubated. Among this one case had concomitant dengue infection and severe complications developed in this patient included meningoencephalitis, hepatic derangement with jaundice (bilirubin 7.3), raised PT/INR (21.2/2.54), TLC (21000) and hypotension.

The classical finding of eschar development serves as an important diagnostic clue in cases of scrub typhus. It is noted that varied reports have been reported upon the occurrence of eschar. The presence of eschar can be missed in dark-skinned people and particularly if it is not actively searched for in covered areas of the body.

In our study eschar was noted in 06(16.21%) patients. Our finding is in concordance with another study by Takhar et al[13] (12.1%) and Raman et al[14] (17.6%) of the Rajasthan region. Another study of this region reported that no case presented with eschar development.[4] There are other Indian studies also who have reported lesser incidence rates of eschar in Indian patients 9.5%[15], 10% [16], 12.5%[17] and 13.1%[18]. A higher incidence has been reported from Taiwan (61.9%)[19].

In this study, the most common complications included thrombocytopenia (75.68%), anaemia (48.65%), urinary tract infection (45.95%), abnormal respiratory system findings (40.54%), encephalitis (27.03%) and splenomegaly (24.32%). The comparison of groups showed that with coinfection presented with more severe deranged laboratory reports; severe complications involving CNS, respiratory system and the urinary system was also more frequent in group with coinfections . Abnormal USG abdomen findings, shock, assisted ventilation and MODS were also more frequent in group with coinfection.

The mortality rate in scrub typhus has shown variation among different countries and regions and is higher among untreated cases [2,20,21]; various reports ranged from 0%[26] to 35%. Overall mortality in our study was in 5 cases (13.51%). It is noteworthy here that all the case fatality occurred in group with coinfection. The reason could be due to the additive pathophysiology of different pathogens and/or supplemented by drug resistance. Among these five cases ST+DV+PV was seen in 2 cases, ST+DV in one, ST+PV in one and ST+TB in one case respectively

There was no case fatality seen in without coinfection; this could be due to the effect of treatment dispersed at the tertiary care centre. All scrub typhus patients were treated with doxycycline, azithromycin and other symptomatic treatment.Hence it can be inferred that concomitant *Dengue virus* or *Plasmodium vivax* infection has led to overall additive pathological effect which further caused organ dysfunction and ultimately death.

Conclusion

The concomitant infection as discussed here could be due to different habitat for vector and the comorbidity of these infections has still not been well documented and there is a need for research to study the impact of concomitant infections.[22].The efforts of government health agencies should be to eradicate scrub typhus disease before it becomes endemic and this can be helped by developing a vaccine, increasing the awareness among physicians, and making rapid, cheap diagnostic tools available .

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