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Observational Study from
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Concurrent Coinfections in Tropics: A Hospital-Based Observational Study from Himachal Pradesh, India

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Abstract

India is the epicenter of tropical fever diseases. Large numbers of cases are diagnosed with scrub typhus, leptospirosis, malaria, dengue, chikungunya, and enteric fever. Coinfections as an etiology of acute undifferentiated fever (AUF) have been recently recognized. The objective of this study was to assess the prevalence of coinfections in patients admitted with AUF in a tertiary-care hospital in the rural setting of Himachal Pradesh, India. Patients with coinfections as an etiology of AUF were the subjects of the study. The clinical records of patients diagnosed with coinfections between July 2018 and October 2018 were analyzed retrospectively in this hospital-based cross-sectional study. Standard protocol and guidelines were followed for the case definitions. Among total patients of 1005 with AUF, 14 (1.39%) patients were found to have coinfections. The most common coinfection was scrub typhus with leptospirosis and was diagnosed in seven (50%) patients. Other coinfections were scrub typhus with dengue in four (29%) and one patient each with scrub typhus and tubercular meningitis, scrub and influenza A (H1N1/2009) infection, and scrub and malaria (*P. falciparum*). Scrub typhus was the most common etiological diagnosis for the AUF and was observed in 159 (15.8%) patients. All the patients with coinfections had scrub typhus as the common infection. The prevalence of coinfections among scrub typhus patients constituted 8%. In tropical regions, coinfections are not very rare. High clinical suspicion for coinfections is required. Syndromic approach in the management is justified.

Keywords: Fever; Tropics; Coinfections.

1. INTRODUCTION

People living in tropical countries suffer from acute febrile illnesses mostly in the monsoon and post-monsoon period. Most of these fevers are transmitted by arthropod vectors. Mosquito species such as the *Anopheles*, *Culex*, and *Aedes*; ticks; and mites are responsible for the transmission of most vector-borne diseases. With a favorable environment, the vectorial capacity increases: the larvae take a shorter time to mature, adult vectors digest blood faster and feed more frequently, and consequently there is a greater capacity to produce more offspring during the transmission period. The extrinsic incubation period of microorganisms and parasites is reduced, thereby increasing the proportion of infective vectors [1]. Thus, high prevalence of infective vectors, increased human vector contact, temperature, humidity, prolonged rains, stagnant water, floods, abundant growth of vegetation, sleeping habits of humans, density, and biting patterns of vectors turn the milieu favorable for disease transmission [2]. Seasonal trend analysis of fever cases seeking health-care services have revealed an increasing trend of acute undifferentiated fever (AUF) illness during and after the monsoon period in the sub-Himalayan state of Himachal Pradesh [3]. Scrub typhus is the leading cause of acute febrile illness in Himachal Pradesh [4]. In the differential diagnosis of AUF, scrub typhus is considered in all the patients in this region. Dengue fever and leptospirosis is increasingly being reported from this part of India [5-8]. With common vectors for tropical fevers and favorable dynamics of infectious disease transmissions existing during the monsoon and post-monsoon time, the coinfections are expected to be more common and are possibly underdiagnosed. Coinfections as an etiology of AUF in patients of this region have been reported scarcely in the literature [2]. The primary objective of this study was to assess the prevalence of the concurrent coinfections among patients with acute febrile illness admitted in a tertiary-care hospital in the rural setting of Himachal Pradesh, India.

2. METHOD(S)

2.1 Study Settings: The study was carried out in the department of medicine of a tertiary-care referral hospital located in the Kangra district of Himachal Pradesh. The hospital receives patients from the lower hills of Kangra, Una, Hamirpur, Mandi,

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and Chamba districts. Most population residing in these areas are involved in agriculture activities. The region experiences subtropical monsoons. The average rainfall is 152 cm (60 inches). The highest rainfall occurs in the Kangra district. During the rainy season, areas at lower altitudes have an average temperature of 20-35°C, which is conducive to the spread of arthropod vectors.

2.2 Patient Selection: Recruitment of patients was done from July 1, 2018, to October 31, 2018, the monsoon and post-monsoon period. All the patients above the age of 18 years fulfilling the definition of AUF and positive for coinfections were included in the study. Inclusion criteria of AUF included fever of 2 weeks or shorter in duration, with lack of localizable or organ-specific clinical features in the patients. Coinfections were defined as the presence of two or more concurrent infective etiologies of AUF. The case definitions of scrub typhus, dengue fever, leptospirosis, malaria, chikungunya, tubercular meningitis, and influenza A (H1N1) were as per the standard guidelines [9-15]. The recorded data of patients were entered in proforma including clinical presentation, examination findings, laboratory investigations, serological, and radiological results. Enzyme-linked immunosorbent assay (ELISA) assay was used to measure scrub typhus and chikungunya-specific IgM levels (InBios International Inc, USA). Dengue fever was diagnosed by ELISA-based NS1 detection and IgM Capture (RecombiLISA, USA). IgM-based immunoassay was used for the diagnosis of leptospirosis (SD Bioline, Republic of Korea). Influenza A (H1N1/2009) was diagnosed by real-time reverse transcriptase polymerase chain reaction (RT-PCR). Microscopic examination of both thick and thin smear was done in the department of pathology for confirmation of malaria. The data obtained were entered in a Microsoft Excel sheet and analyzed with statistical software SPSS 21.0 (IBM Corp., Armonk, NY, USA). Qualitative data were calculated in the form of frequency and percentage. Quantitative data were presented as mean \pm standard deviation (SD). The study was approved by the institutional ethics committee.

3. RESULTS

During the study period, 1005 patients were admitted with the diagnosis of AUF in the medicine wards. Month-wise trend of AUF is shown in Figure 1.

The analysis of the seasonal trend shows the maximum cases reported in the months of August, September, and October. The increase in the number of patients diagnosed with AUF also coincided with a concurrent increase in scrub typhus during the same period as shown in Figure 2.

A total of 159 cases were diagnosed with scrub typhus from July to October. Concurrent coinfections were diagnosed in 14 (1.3%) patients. All the patients diagnosed with coinfections had scrub typhus as a common infection. The prevalence of coinfection among scrub typhus patients was 8.8% (14/159). The distribution of coinfections is shown in Table 1.

The most common coinfection observed was scrub typhus with leptospirosis in seven patients. Among them, five were males, and two were females. All of them had hyperbilirubinemia, transamininitis, hypoalbuminemia, and renal dysfunction. Aspartate transaminase (AST) levels were higher than alanine transaminase (ALT) levels across all the patient groups. Meningism and encephalopathy were present in three patients with scrub typhus and leptospirosis; in one with scrub and dengue fever; and in one patient with tubercular meningitis, scrub typhus, and dengue fever coinfection. Degrees of elevation of liver enzymes were higher in scrub typhus and leptospirosis group compared to others as shown in Table 1. Renal dysfunction was in the form of acute kidney injury (AKI), and none of the patients required renal replacement therapy. Acute respiratory distress syndrome (ARDS) was also more common in the scrub typhus and leptospirosis group. Among seven patients with

Figure 1: Monthly trend analysis of AUF cases admitted in the year 2018.

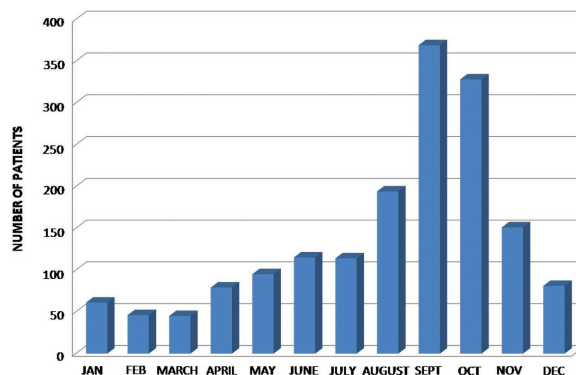
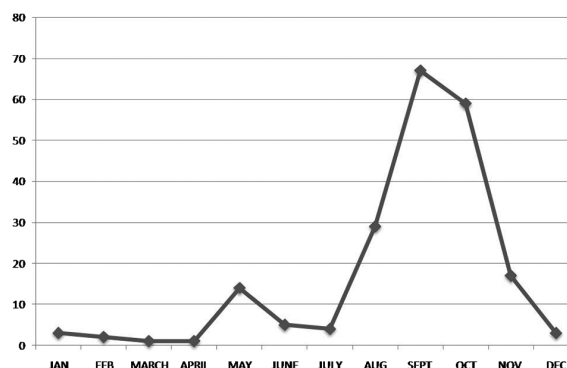


Figure 2: Monthly trend analysis of scrub typhus cases admitted in the year 2018.**Table 1: Demographic, hematological, and biochemical parameters of coinfections groups.**

Parameters	S + L (n = 7)	S + D (n = 4)	S + H1N1 (n = 1)	S + TBM + D (n = 1)	S + M (n = 1)
Age (years)	32 ± 11.4	35 ± 7.5	43	41	37
Gender	M = 5 F = 2	M = 2 F = 2	F	M	M
GCS	12 ± 3	14 ± 1	15	8	15
SBP (mm of Hg)	95.7 ± 9.62	118.5 ± 10.5	106	116	126
DBP (mm of Hg)	65.1 ± 7.10	85 ± 10.1	86	74	88
RR (/minutes)	24 ± 6	18 ± 2	34	18	22
PR (per minute)	109.4 ± 8.6	89 ± 9.5	116	86	98
Hb (g/dL)	10.7 ± 1.2	12.1 ± .87	13	9.6	8.5
TLC (per mm ³)	15,800 ± 5630	9600 ± 1320	6750	4700	3680
Platelet (per mm ³)	78,028.5 ± 28,130.7	42,500 ± 19,122.4	97,000	87,000	54,000
BUN (mg/dL)	36.8 ± 11.1	25.5 ± 3.41	14	17	19
Creatinine (mg/dL)	2.02 ± 0.45	1.47 ± .29	1.2	1.7	.9
Bilirubin (mg/dL)	7.82 ± 2.85	2.05 ± .723	1.3	2.1	1.4
AST (U/L)	551.8 ± 486.1	129 ± 18	228	168	143
ALT (U/L)	231.8 ± 238.7	71.5 ± 6.6	154	76	58
ALP (U/L)	318 ± 163.5	159 ± 34.4	148	180	113
Albumin (g/dL)	2.51 ± .39	2.9 ± .43	3.0	2.9	3.5
PaO ₂ /FiO ₂	193 ± 40.86	256.2 ± 30.18	166	320	326
Sodium (mmol/L)	128.2 ± 8.15	138.2 ± 4.0	129	127	131
Potassium (mmol/L)	4.11 ± .86	4.62 ± .35	4.6	3.8	4.5
Lactate (mmol /L)	3.3 ± 2.5	1.4 ± .6	2.1	1.2	1.4

Key: n—number; S—scrub typhus; L—leptospirosis; D—dengue; M—malaria; H1N1—influenza A (H1N1/2009); TBM—tubercular meningitis; M—male; F—female; GCS—Glasgow coma scale; SBP—systolic blood pressure; DBP—diastolic blood pressure; RR—respiratory rate; PR—pulse rate; Hb—hemoglobin; TLC—total leucocyte count; BUN—blood urea nitrogen; AST—aspartate transaminase; ALT—alanine transaminase; ALP—alkaline phosphatase; PaO₂—partial pressure of oxygen; FiO₂—fraction of inspired oxygen

scrub typhus and leptospirosis, one male patient had pulmonary hemorrhage. Scrub with influenza A H1N1/2009 coinfection patient also presented with ARDS, whereas the dengue, scrub typhus, and tubercular meningitis patient presented with jaundice and encephalopathy. Lactate was higher in scrub leptospirosis coinfection patient attributable to end organ hypoperfusion and renal dysfunction. Thrombocytopenia was a consistent finding across all the groups but was more pronounced in the scrub and dengue coinfection. Eschar was present in one patient with scrub and leptospirosis. The patient with scrub with malaria was a resident of Gujarat, India. Hepatosplenomegaly was present in three patients among scrub typhus and leptospirosis coinfection and in one patient in the scrub typhus and dengue group. Massive splenomegaly was observed in the patient having scrub typhus and malaria, and mild splenomegaly was seen in a patient among the scrub typhus and leptospirosis group. All the patients improved clinically except one patient who had scrub typhus and leptospirosis coinfection and died due to pulmonary hemorrhage.

4. DISCUSSION

Coinfections as a cause of acute undifferentiated fevers are an emerging phenomenon in tropical countries [16]. Malaria, dengue, and chikungunya are the most common coinfections reported from India [17]. Scrub typhus, malaria, dengue fever, and leptospirosis coinfections have been reported from Himachal Pradesh, Uttarakhand, central India, Puducherry, and also from other parts of India [2,18-22]. The prevalence of coinfections among patients with AUF was 1.39% in this study. Similar results have been observed in other studies [2,23]. Scrub typhus was diagnosed as the common infection in all the 14 cases in this study. Rickettsial diseases have been increasingly recognized in most regions of India. Scrub typhus is the most commonly occurring rickettsial infection in India. Leptospirosis is a seasonal disease, and outbreaks coincide with that of dengue fever, chikungunya fever, malaria, and scrub typhus. The diagnosis of scrub typhus and leptospirosis is based on imported commercially available IgM ELISA, which use cutoffs derived from low endemicity areas. The possibility of cross-reactivity of various serological tests for leptospirosis and scrub typhus cannot be ruled out. Data on cross-reactivity of various serological tests among these infections are limited. While analyzing serological and PCR-based molecular assays, molecular confirmation of scrub typhus and leptospirosis coinfection was established in only 1 among 10 IgM ELISA positive cases [24]. Clinical diagnosis of coinfections is complex in patients with AUF, as the initial symptoms, signs, and laboratory investigations overlap as is evident in our study. The clinical symptoms and signs were nonspecific except in one patient where eschar was present. Little is known about the clinical significance of coinfections as compared to mono-infections. Conflicting reports about the severity of illness have been observed in different studies [18,25,26]. We could not draw any conclusion on the clinical significance of concurrent coinfections in our study, as mono-infections were not studied as controls. Coinfections have been a retrospective diagnosis in majority of the reported literature.

5. CONCLUSION

In the resource-limited settings, it is rational to follow a syndromic approach while treating AUF. The knowledge of the epidemiological aspects of tropical fevers in a particular geographical region helps in presumptive diagnosis and treatment pending investigations. It may be prudent to test for the entire differential diagnosis in patients with AUF during monsoons and post-monsoons if the local epidemiology is unknown. Coinfections can be a serious public health issue in tropical countries. The coinfections should be more common than reported in the literature. Studies should be designed for determining the clinical significance of coinfections in comparison to mono-infections. Emphasis must be laid on the confirmation by molecular assay to rule out cross-reactivity. It is also necessary to develop a robust local population-based seroprevalence data based on the serological tests.

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Author Contributions

SR and RS conceived and designed the study; SM, BDN, KD, KB, and BS collected the data; SM, BDN, KD, KB, BS, SR, and RS analyzed the data; and SM, BDN, KD, KB, BS, SR, and RS prepared the manuscript.

Conflict of Interest

None.

References

1. Rueda LM, Patel KJ, Axtell RC, Stinner RE. Temperature-dependent development and survival rates of *Culex quinquefasciatus* and *Aedes aegypti* (Diptera: Culicidae). *J Med Entomol.* 1990; 27: 892-8.
2. Sharma P, Singh M, Gandhi MK, Raina S, Raina SK, *et al.* Seasonal trend of fever cases seeking health care services at a tertiary care centre— an audit of retrospective data from sub-Himalayan region. *J Evolution Med Dent Sci.* 2018; 7: 1862-7.
3. Raina S, Raina RK, Agarwala N, Raina SK, Sharma R. Co-infections as an aetiology of acute undifferentiated febrile illness among adult patients in the sub-Himalayan region of north India. *J Vector Borne Dis.* 2018; 55: 130-6.
4. Varghese GM, Janardhan J, Mahajan SK, Tariang D, Trowbridge P, *et al.* Molecular epidemiology and genetic diversity of *Orientia tsutsugamushi* from patients with scrub typhus in three regions of India. *Emerg Infect Dis.* 2015; 21: 64-9.
5. Verma S, Kanga A, Singh D, Verma GK, Mokta K, *et al.* Emergence of travel: associated dengue fever in a nonendemic, hilly state. *Adv Biomed Res.* 2014; 3: 239.
6. Jaryal SC, Chauhan S, Thakur K, Sood A, Kashyap N. Never ending challenge of dengue Current scenario in the hilly state of north India. *Nat J Lab Med.* 2016; 5: MO11-4.
7. Chauhan V, Mahesh DM, Panda P, Mokta J, Thakur S. Profile of patients of leptospirosis in sub-Himalayan region of north India. *J Assoc Physicians India.* 2010; 58: 354-6.

8. Chauhan V, Thakur S. Leptospirosis in sub-Himalayan region: a neglected entity. *Indian J Med Microbiol.* 2016; 34: 390-409.
9. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHRICMR guidelines for diagnosis and management of rickettsial diseases in India. *Indian J Med Res.* 2015; 141: 417-22.
10. *Dengue National Guidelines 2014.* Delhi: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Available from: <http://www.nvbdc.gov.in/Doc/Dengue-National-Guidelines-2014.pdf> (accessed on June 30, 2018).
11. *National treatment guidelines for antimicrobial use in infectious diseases.* Delhi: National Centre for Disease Control. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Available from: <http://www.ncdc.gov.in/writereaddata/mainlinkfile/File558.pdf> (accessed on June 30, 2018).
12. *National guidelines for clinical management of chikungunya 2016.* Delhi: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Available from: <http://nvbdc.gov.in/Doc/National-Guidelines-Clinical-Management-Chikungunya2016.pdf> (accessed on June 30, 2018).
13. *Guidelines for diagnosis and treatment of malaria in India 2014.* Delhi: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Available from: <http://nvbdc.gov.in/Doc/Guidelines-Malaria-Diagnostic-Treatment-2014.pdf> (accessed on June 30, 2018).
14. Ministry of Health and Family Welfare, India information on swine flu, New Delhi. MOHFW.] Available from: <http://mohfw-h1n1.nic.in/document.pdf> (accessed on June 30, 2018).
15. Marais S, Thwaites G, Schoeman JF, Torok ME, Misra UK, *et al.* Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis.* 2010; 10: 803-12.
16. Salam M, Mustafa S, Hafiz A, Chaudhary AA, Deeba F, *et al.* Global prevalence and distribution of coinfection of malaria, dengue and chikungunya: a systematic review. *BMC Public Health.* 2018; 18: 710.
17. Yeolekar ME. Tropical infections: Clinical implications. *J Assoc Physicians India.* 2018; 66: 68-9.
18. Ahmed S, Dhar M, Mittal G, Bhat NK, Shirazi N, *et al.* A comparative hospital based observational study of mono and coinfections of malaria, dengue virus and scrub typhus causing acute undifferentiated fever. *Eur J Clin Microbiol Infect Dis.* 2016; 35: 705-11.
19. Shelke YP, Deotale VS, Maraskolhe DL. Spectrum of infections in acute febrile illness in central India. *Indian J Med Microbiol.* 2017; 35: 480-4.
20. Basheer A, Iqbal N, Mookkappan S, Anitha P, Nair S, *et al.* Clinical and laboratory characteristics of dengue-orientia *tsutsugamushi* coinfection from a tertiary care center in south India. *Mediterr J Hematol Infect Dis.* 2016; 8: e2016028.
21. Morch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, *et al.* Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. *BMC Infect Dis.* 2017; 17: 665.
22. Borkakoty B, Jakharia A, Biswas D, Mahanta J. Co-infection of scrub typhus and leptospirosis in patients with pyrexia of unknown origin in Longding district of Arunachal Pradesh in 2013. *Indian J Med Microbiol.* 2016; 34: 88-91.
23. Mittal G, Ahmad S, Agarwal RK, Dhar M, Mittal M, *et al.* Aetiologies of acute undifferentiated febrile illness in adult patients: an experience from a tertiary care hospital northern India. *J Clin Diagn Res.* 2015; 9: DC22-4.
24. Gupta N, Chaudhry R, Mirdha B, Das B, Dar L, *et al.* Scrub typhus and leptospirosis: The fallacy of diagnosing with IgM enzyme linked immunosorbant assay. *J Microb Biochem Technol.* 2016; 8: 071-5.
25. Londhey V, Agrawal S, Vaidya N, Kini S, Shastri JS, *et al.* Dengue and chikungunya coinfections: The inside story. *J Assoc Physicians India.* 2016; 64: 36-40.
26. Barua A, Gill N. A comparative study of concurrent dengue and malaria infection with their mono-infection in a teaching hospital in Mumbai. *J Assoc Physicians India.* 2016; 64: 49-52.