

Clinical and Laboratory Characteristics of Patients with Mono and Coinfection of Dengue and Scrub typhus

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ABSTRACT

Background: Dengue is a neglected tropical disease, and Scrub typhus is an emerging tropical illness in Nepal. Coinfection between them is found in literature and clinical practice. The objective of this study is to describe and compare the demographic, clinical, and laboratory characteristics of patients with mono and coinfection of Dengue and Scrub typhus.

Methods: This was a single-center hospital-based retrospective study, performed at Beni District Hospital, Nepal. The patient who was diagnosed with mono and coinfection of Dengue and Scrub typhus from 1st January 2020 to 16th September 2020 were included. Data regarding demographic characteristics, symptoms, signs, and laboratory parameters were collected and analyzed.

Results: In 53 patients who fall under the inclusion criteria of our study, 12 patients had coinfection with dengue and Scrub typhus with headache being the most common symptom regardless of mono or coinfection followed by myalgia and arthralgia. Total platelet counts at the time of admission were lower in the coinfection group with increasing thrombocytopenia during the disease course in comparison to mono-infection. The maximum temperature recorded, elevation in hepatic enzymes, and duration of defervescence were more in the coinfection group in comparison to dengue and scrub mono-infection.

Conclusions: Mono and coinfection of Dengue, Scrub typhus present with common clinical symptoms, laboratory findings. With limited resources for screening and diagnosis, clinical prediction based on symptoms alone or together with lab parameters is difficult which is further difficult in the presence of Co-infection.

Keywords: Clinical; coinfection; dengue; laboratory parameter; scrub typhus

INTRODUCTION

Dengue and Scrub typhus are rapidly emerging tropical infectious diseases in the world as well as in Nepal.¹ Dengue is a systemic viral disease caused by the dengue virus, genus *Flavivirus* and is transmitted by the bite of infected female *Aedes aegypti* and *albopictus* mosquito.² Scrub typhus is a vector-borne zoonotic disease caused by *Orientia tsutsugamushi*, an obligate intracellular gram-negative bacterium from the *Rickettsiaceae* family.

Both diseases have similar clinical presentation, seasonal occurrence, and lab profiles causing diagnostic and therapeutic dilemma.^{3,4} Coinfection between them though rare can be found in a clinical setting, especially

in epidemic season.⁵ This study aims to explore common clinical and lab parameters of mono and co-infection of Dengue, Scrub typhus, with demographic, clinical, and laboratory parameters.

METHODS

This was a single-center hospital-based observational retrospective cross-sectional study performed at Beni Hospital, a district-level hospital in Gandaki province of Nepal. Ethical approval was taken from the Hospital administration and Nepal health research Council, Kathmandu (Ref No. 1598). Patients were explained about the study and informed written consent was obtained. Inclusion criteria included patients admitted at

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Beni Hospital and diagnosed with dengue, Scrub typhus, and dengue-scrub co-infection by rapid diagnostic kit from January 2020 to September 2020. Exclusion criteria included patients with incomplete hospital records, patients with pre-existing hepatic, renal, and hematological disorders, patients with HIV/AIDS, and patients taking drugs affecting hematological and liver functions. Rapid diagnostic tests (RDTs) kit was “Dengue Day 1Test” manufactured by J. MITRA & CO. PVT. LTD India for Dengue and “InBios Scrub typhus for DetectTM IgM ELISA” manufactured by InBios International, Inc. America was used for Scrub typhus. A purposive sampling technique was used and there was a total of 110 patients of Dengue and Scrub as reported by Hospital to EWARS. However, only 53 patients were admitted in the hospital during this period and were included in the study. Among 53 patients, 19 patients had mono-infection with Dengue, 22 had Scrub typhus mono-infection, and 12 has dengue and Scrub typhus coinfection.

Data were entered in Microsoft Excel 13 and analyzed using IBM SPSS 26.0. For demographic and clinical signs and symptoms, descriptive analyses and Chi-square test were used. One-way ANOVA was applied for comparing the means of the three groups. The result was considered significant if the p-value was less than 0.05.

RESULTS

Out of the 53 patients, 19 patients had dengue, 22 patients had Scrub typhus and 12 patients had co-infection with dengue and Scrub typhus. The mean age of patients was 38.11 years, 33.86 years, and 23.66 years in dengue mono-infection, scrub mono-infection, and dengue scrub coinfection respectively. Headache was the most common symptom occurring in 50 patients regardless of mono or coinfection. Headache was present in all patients (100%) with dengue mono-infection followed by arthralgia (89.5%), retro-orbital pain (78.9%), myalgia (63.2%), and Nausea (63.2%). Similarly, in scrub mono-infection, headache (95.5%) was followed by myalgia (72.7%), anorexia (72.7%), nausea (68.2%), and hepatomegaly (45.5%). However, headache (83.3%), myalgia (75%), nausea (75%), anorexia (75%), and retro-orbital pain (75%) occurred in coinfection as shown in Table 1.

Eschar was more common in patients with Scrub typhus mono-infection (18.2%) and co-infection (16.7%) but none in dengue mono-infection. Arthralgia and retro-

orbital pain were present statistically significant in Dengue (Table 1).

Table 1. Clinical Characteristics in Patients with Dengue, Scrub typhus and their co-infection.

Parameter	Dengue N= 19	Scrub typhus N=22	Co- infection N=12	p Value*
Headache	19 (100%)	21 (95.5%)	10 (83.3%)	0.141
Myalgia	12 (63.2%)	16 (72.7%)	9 (75.0%)	0.726
Arthralgia	17 (89.5%)	8 (36.4%)	6 (50%)	0.002
Retro orbital pain	15 (78.9%)	7 (31.8%)	6 (50%)	.010
Cough	2 (10.5%)	3 (13.6%)	3 (25%)	.531
Nausea	12 (63.2%)	15 (68.2%)	9 (75%)	.789
Vomiting	3 (15.8%)	9 (40.9%)	6 (60%)	.098
Anorexia	11 (57.9%)	16 (72.7%)	9 (72%)	.500
Abdominal pain	8 (42.1%)	7 (31.8%)	6 (50%)	.563
Eschar	0	4 (18.2%)	2 (16.7%)	.150
Lymphadenopathy	1 (5.3%)	4 (18.2%)	3 (25%)	.284
Hepatomegaly	4 (21.1%)	10 (45.5%)	5 (41.7%)	.238
Splenomegaly	1 (5.3%)	9 (40.9%)	3 (25%)	0.30

*Chi-Square Test

The laboratory parameters were analyzed and were found as shown in Table 2. The mean duration of hospital stay and duration of fever were longer in the Dengue Scrub typhus coinfection group. Total platelet counts at the time of admission were along the lower borderline for dengue and coinfection whereas they were within the normal limit for Scrub typhus. During hospital admission, total platelets counts dramatically decreased in patients with dengue and coinfection whereas they were within normal limits for Scrub typhus. Liver function tests revealed a more than threefold rise in both Aspartate aminotransferase and Alanine aminotransferase in more than half of patients with dengue mono-infection and coinfection with dengue and Scrub typhus.

Table 2. Comparison of laboratory findings in patients with Dengue, Scrub typhus, and Coinfection.

Parameter	Dengue N=19	Scrub typhus N=22	Coinfection N=12	p Value *
Duration of Stay (in days)	3.53 (2.19)	3.55 (1.057)	4.75 (2.221)	.136
Total Duration of fever (in days)	4.74 (2.8)	5.14 (3.07)	5.75 (2.56)	.635
Maximum temperature (in Fahrenheit)	101.86 (0.82)	102 (0.91)	102.1 (1.120)	.555
Hemoglobin (in gm/dl)	13.27 (2.450)	13.02 (1.53)	13.1 (1.77)	.919
Total Count (in cells/mm ³)	7557.89 (2681.27)	9204.54 (4214.31)	8800 (2859.75)	.305
Neutrophil	60.84 (13.39)	66.18 (13.79)	67.58 (12.36)	.308
Lymphocyte	32.84 (13.49)	29.41 (13.38)	25.08 (13.97)	.306
Platelets at admission (in thousand /mm ³)	150.21 (80.18)	180.72 (87.44)	130.75 (90.63)	.242
Minimum platelets(in thousand/ mm ³)	143.26 (78.086)	162.72 (79.56)	125.83 (91.51)	.443
Urea (mg/dl)	25.43 (13.01)	39.40 (27.73)	29.66 (7.26)	0.81
Creatinine (mg/dl)	1.06 (.22)	1.2 (0.42)	1.11 (0.34)	.398
Sodium (mmol/L)	122.20 (4.88)	129.51 (4.14)	129.71 (6.47)	0.50
Potassium (mmol/L)	3.74 (0.35)	3.53 (0.38)	3.64 (0.31)	.208
Total bilirubin (mg/dl)	1.55 (1.12)	1.06 (0.38)	1.59 (1.45)	.192
Direct bilirubin (mg/dl)	0.63 (0.81)	0.35 (0.27)	0.40 (0.29)	.223
Alanine Aminotransferase (U/L)	95.95 (70.22)	125.77 (96.48)	114.83 (64.11)	.504
Aspartate Aminotransferase(U/L)	84.46 (61.49)	118.32 (90.72)	114.92 (52.65)	.308
Alkaline Phosphatase (U/L)	254.47 (115.50)	313.54 (212.13)	306.08 (103.52)	0.476
Days of Defeverescence	2.26 (0.99)	2.09 (0.68)	2.92 (1.62)	0.099

*One- way ANOVA

DISCUSSION

Tropical Infection is a common but underdiagnosed and underestimated health problem with epidemic potential. Dengue is the topmost mosquito-borne viral disease in 2012 with a 30-fold increase in global incidence over the past 50 years and represents a global pandemic threat.⁶ This infection commonly occurs in the post-monsoon season.⁷ Nepal lies in the Tsutsugamushi triangle where Scrub typhus is endemic.^{8,9} Scrub typhus needs to be included in the differential diagnosis of patients presenting with acute febrile illness even in the absence of characteristic eschar. A high index of clinical suspicion should be kept, particularly during outbreaks where the diagnosis can be missed. Timely diagnosis and appropriate management can prevent fatal outcomes associated with Scrub typhus.¹⁰ Clinically both diseases present with fever with similar clinical manifestations including headache myalgia, arthralgia, weakness, anorexia, nausea, and vomiting with laboratory findings of thrombocytopenia, with renal and hepatic impairment.

The number of cases is being underreported and underdiagnosed. According to Annual Health Reports 2075/76(2018/2019) which was published in November

2020 by the Department of Health Service, Government of Nepal 3,424 Dengue cases were reported from 44 districts across Nepal with two deaths. Gandaki province has reported 42 cases which were 568 in the previous 2074/75 fiscal year.¹¹ Similarly fact sheets published by the Epidemiology and Disease Control division in the Fiscal year 2076/2077 (From Shrawan 1 to Kartik 18) a total of 14662 cases of Dengue were reported with 24 cases of Dengue Fever from Myagdi District. At the same time, 1239 cases of Scrub typhus were reported.¹¹ Study by Karki et al shows 101 cases of Scrub typhus reported from 16 districts of Nepal in 2015, and 831 cases of Scrub typhus were reported in 2016 From April to December.⁸ Management of Infectious disease is a major challenge especially, in a rural hospital with limited clinical experts and laboratory services. Many infectious communicable diseases (IDs) are endemic in Nepal with around 70 % morbidity and mortality.¹³ In the last 5 years, the incidence of dengue cases has risen alarmingly. The largest-ever outbreak was reported in 2019, with total cases of 14662 in post-monsoon season including six mortalities.¹¹ First Scrub typhus was reported in Nepal in 1981.¹⁵ Studies done by Karki et al. 2017 showed evidence of the circulation of Scrub typhus in Nepal with potential outbreak magnitude .⁸ First outbreak was confirmed in 2015 following an earthquake

with a total of 101 confirmed Scrub typhus cases from 16 districts in Nepal with around an 8% case fatality rate,^{1,8} In 2018, 50 districts reported 1058 Scrub typhus cases in Nepal.

Thrombocytopenia is typically associated with dengue fever but has also been reported in Scrub typhus. In this study, we found that thrombocytopenia was more severe in the coinfection group than in dengue and Scrub typhus alone. Earlier fall and attainment of nadir in platelets count in dengue patients might be an indicator of coinfection with Scrub typhus. Similarly, a more severe picture of thrombocytopenia in patients with Scrub typhus might suggest coinfection with dengue. The hepatic enzymes are the most affected as compared to other liver functions,¹⁶ Alanine aminotransferase levels were found higher than Aspartate aminotransferase levels in all groups. Duration of defeverescence was more in Scrub typhus and dengue coinfection than with dengue scrub mono-infection among patients treated with doxycycline but finding were not statistically significant. The major limitation of our study is its retrospective model and small sample size. Similarly, this study has been conducted only in a hospital-based population. Prior use of antibiotics and the inability to recognize coinfection with other diseases might have confounded our findings. Nonetheless, the fundamental strength of our study was well-documented clinical and laboratory findings in all patients presenting with febrile illness during the study period. Resources constraint is always a problem in the health sector. Many primary care facilities still lack definite laboratory services for the diagnosis of various common health problems. Many physicians use epidemiological patterns along with clinical and basic laboratory services including blood count and liver function tests. Recognizing clinical and laboratory features with timely diagnosis in dengue and scrub coinfection might help in reducing fatal outcomes.

CONCLUSIONS

Dengue, Scrub typhus, and Coinfection are common causes of tropical fever present with common clinical symptoms, and laboratory findings. With limited resources for testing screening and diagnosis, clinical prediction based on symptoms alone or together with lab parameters is difficult which is further difficult in the presence of Co-infection. The finding of Arthralgia and Retro orbital pain is more with Dengue infection. Clinical finding of eschar predicts Scrub or Coinfection of dengue and Scrub. A larger prospective study is needed for further conclusion in clinical profile, and laboratory findings to differentiate between mono and coinfection of dengue and Scrub typhus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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