

Seropositivity for dengue and *Leptospira* IgM among patients with acute febrile illness: an indicator of co-infection?

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Abstract

Introduction Presentation of febrile illness with nonspecific features, overlapping manifestations of dengue and leptospirosis, limited laboratory diagnostic tests, make the clinical diagnosis of pyrexia a challenge. The present study aimed to determine the prevalence of *Leptospira* and dengue IgM co-infection among acute febrile illness patients.

Methods This is a retrospective hospital-based study which included patient data collected from June 2016 to May 2017. Inpatients' samples (n=2139) were tested for dengue and/or *Leptospira* IgM at the Microbiology Laboratory. Data like duration of fever, platelet count, hemoglobin, white blood cell count, erythrocyte sedimentation rate, results of liver and renal function tests, mode of treatment, were collected from medical records of laboratory-confirmed co-infection cases.

Results Among 1612 serum samples tested for dengue IgM by ELISA, 382 (23.7%) were positive, 17 equivocal and 1213 were negative. Of the 811 *Leptospira* IgM ELISA done, 119 (14.7%) were positive, 17 equivocal and 675 negative. Two hundred eighty-four samples were tested for both infections and nine (3.2%) were positive for both and 275 were negative. These nine patients positive for dual infections showed elevated transaminases, alkaline phosphatase, serum bilirubin, creatinine, and blood urea, thrombocytopenia and leukocytosis. They received effective antibiotics along with supportive treatment and were cured of the infection.

Conclusions The study emphasizes the possibility of leptospirosis and dengue co-infection (3.2%) and need for confirmation by a highly specific test like PCR. If co-infection is suspected, treatment with specific antibiotics for leptospirosis and supportive treatment for dengue is mandatory, with due attention to complexity of organ involvement.

Keywords Leptospirosis, dengue, co-infection, IgM ELISA, febrile illness.

Introduction

In tropical countries, patients with diseases like malaria, leptospirosis, dengue and typhoid present with acute undifferentiated fever.¹

Presentation of febrile illness with nonspecific features and limited laboratory diagnostic tests make the clinical diagnosis a challenge to the physicians, as they must rule out co-infections.² Dengue has been rampant in India in the past few years, and the overall prevalence of laboratory-confirmed dengue is 38.3% as reported by earlier works.³ Every year more than 100,000 people are infected by dengue in India, of which 15,000 cases are from the state of Karnataka.⁴ Leptospirosis, an under-reported zoonotic disease is treatable with antibiotics if diagnosed early. In India, the annual mortality of leptospirosis is around 19.7 cases per 100,000 population.⁵

There are several laboratory tests available for the diagnosis of leptospirosis and dengue. Screening tests for leptospirosis include IgM based assays (ELISA, immuno-dot and lateral flow) which are cost-effective, easy to perform and

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available in most of the laboratories. However, their results should be confirmed by confirmatory tests like microscopic agglutination test (MAT) or polymerase chain reaction (PCR).⁶ For presumptive diagnosis of dengue infection, IgM capture ELISA is used and can be confirmed with a nucleic acid amplification test (NAAT). Plaque reduction neutralization test (PRNT) can be used to eliminate cross-reaction with other flaviviral infections. However, NAAT and PRNT are available only in reference laboratories.⁷

There have been reports of co-infection with *Leptospira*, and dengue from Tamil Nadu, Andhra Pradesh and Kerala.⁸⁻¹⁰ Mangalore is endemic for dengue and leptospirosis. In this area, the reported leptospirosis fatality rate is around 3.7% and three serotypes of dengue virus (DEN-1, 2 and 3) are known to cause disease.^{11,12} However, there are no published reports on the seroprevalence of leptospirosis and dengue co-infection from this region. Hence, the present study helps to determine the proportion of *Leptospira* and dengue IgM seropositivity and the outcome of the patients with co-infection.

Methods

This is a retrospective hospital record-based study which includes patient's data collected from June 2016 to May 2017 from 850 bedded Kasturba Medical College Hospital (KMCH), Mangalore, India, which is a tertiary care hospital. Patients admitted to KMCH during the study period who had laboratory confirmed leptospirosis and dengue were included in the study. The study was conducted after obtaining approval from the Institutional Ethics Committee, KMC, Mangalore. All inpatient blood samples (n=2139) from KMCH that were received and processed for dengue and *Leptospira* IgM by ELISAs at the Microbiology Laboratory during the period were included in the study. All outpatient samples were excluded from the study. Panbio Dengue virus IgM capture ELISA (Alere, Australia) and Panbio *Leptospira* IgM ELISA (Inverness Medical Innovations, Australia) kits were used by the laboratory to test for IgM antibodies for dengue and *Leptospira*. Results of ELISA were reported as negative (<9 Panbio

units), equivocal (9-11 Panbio units) and positive (>11 Panbio units). The sensitivity of *Leptospira* IgM ELISA is 90.8% and its specificity is 95.1% as reported by Sengupta et al. (2018).¹³ The sensitivity and specificity of dengue IgM ELISA is 87% and 72.2% respectively.¹⁴

Primary data collected from the laboratory information system (LIS) included results of dengue and *Leptospira* IgM ELISA. Patients (n=9) with positive results for both *Leptospira* and dengue IgM ELISA (>11 Panbio units), other relevant details like duration of fever, blood culture results, seropositivity for human immunodeficiency virus (HIV), hepatitis B, C, and E virus, results of Widal test, Weil Felix test, platelet count, hemoglobin, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), results of liver and renal function tests, mode of treatment were collected from the medical records. Prior permission from the Medical Superintendent of the hospital was obtained to access the medical records.

The data was analysed using statistical package SPSS V.16.0 (SPSS Inc., USA). Continuous variables are reported as mean $\pm$ standard deviation (SD), and categorical variables as percentages. The means of *Leptospira* and dengue IgM antibody levels of mono-infection patients were compared with those of co-infected patients using student's t-test. A p value <0.05 was considered significant.

Results

A total of 1612 serum samples were tested only for dengue IgM ELISA, out of which 382 (23.7%) samples were positive, 17 were equivocal, and 1213 were negative. As many as 811 samples were tested only for *Leptospira* IgM ELISA, of which 119 (14.7%) were positive, 17 were equivocal, and 675 were negative. A total of 284 patient samples were tested for both dengue and *Leptospira* IgM and 9 (3.2%) were positive for both *Leptospira* and dengue IgM, and 275 were negative for both the infections as shown in Figure 1.

Clinical signs and symptoms of *Leptospira* mono-infected patients were: fever, headache, myalgia, vomiting, renal failure. Their other

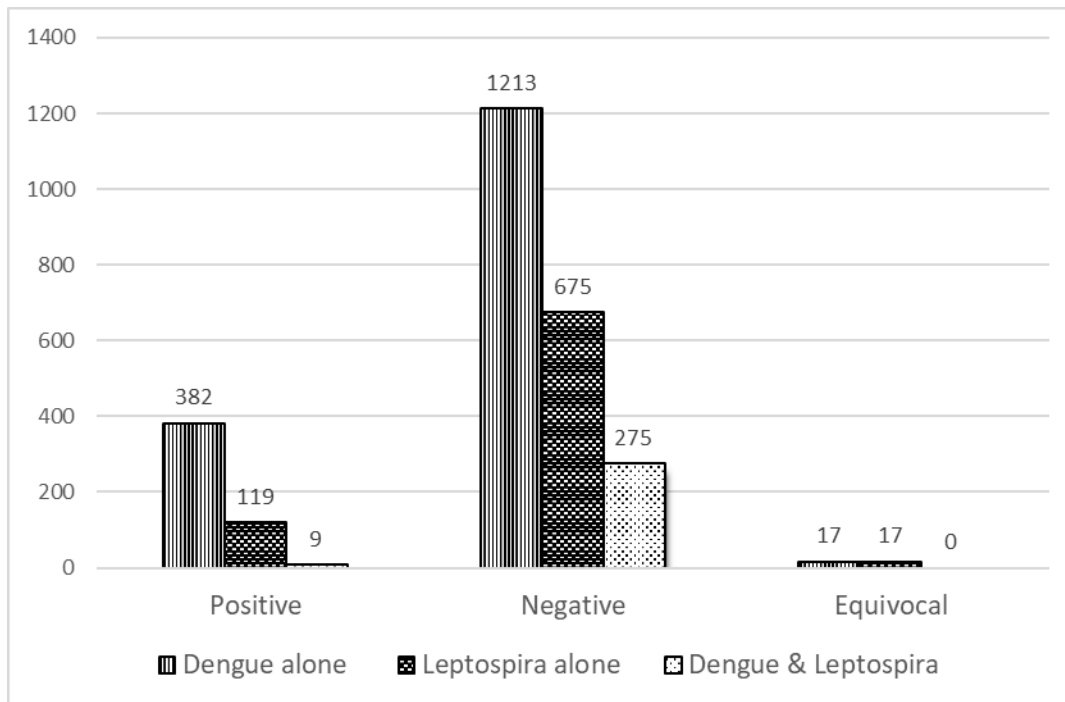


Figure 1. Results of dengue and *Leptospira* IgM ELISA

laboratory test parameters were: increased ESR, WBC count, liver function tests (increased aminotransferase, bilirubin, alkaline phosphatase), impaired renal function tests (increased plasma creatinine) and positive *Leptospira* IgM ELISA (mean value of IgM 22.9 Panbio units and median 22.7).

Clinical signs and symptoms of dengue mono-infected patients were: fever, headache, myalgia rashes, vomiting. Their other laboratory test parameters were: increased ESR, WBC count, liver function tests (increased aminotransferase, bilirubin, alkaline phosphatase), impaired renal function tests (increased plasma creatinine) thrombocytopenia and positive dengue IgM ELISA (mean value of IgM 34 Panbio units and median 33).

Among the 9 co-infected cases, three (33.3%) were females and six (66.7%) were males. The mean age of co-infected patients was 44.78 years. They all had elevated levels of aspartate aminotransferase, alanine aminotransferase, serum bilirubin, creatinine, and blood urea. Blood tests showed thrombocytopenia, leukocytosis and raised ESR. The mean and median value of the laboratory investigations of

these nine patients is shown in Table 1. The mean of *Leptospira* and dengue IgM antibodies of the co-infected patients was 26.0 and 33.6 Panbio units and the median was 22 and 27, respectively. All 9 co-infected patients had variable signs and symptoms as shown in Table 2.

The medical records of these 9 *Leptospira* and dengue co-infected patients had the results of other investigations also. Their blood culture and peripheral smear for malaria, serology for HIV, hepatitis B, C, and E virus, Widal and Weil Felix tests were found to be negative. One among these nine patients was positive for IgM antibodies to hepatitis A virus. Protean clinical presentation of these patients and endemicity of various infections in our area has necessitated the treating physician to order all these investigations. Results of dengue and *Leptospira* IgM, clinical signs and symptoms, antibiotics used for treatment and the outcome of these patients are shown in Table 2.

Discussion

Leptospirosis has fluctuating and nonspecific clinical manifestations. Hence, it is difficult to differentiate clinically from other tropical febrile

Table 1. Laboratory investigation data of co-infected patients (n=9)

Name of investigation	Normal range	Mean $\pm$ standard deviation	Median
Erythrocyte sedimentation rate	1-10 mm/1 st hour	39.7 $\pm$ 24.7	40
White blood cell count	4-10 $\times 10^3$ cells/ mm ³	12.1 $\pm$ 10.4	12.0
Platelet count	150-400 $\times 10^3$ cells/mm ³	82.0 $\pm$ 48.9	107.0
Serum bilirubin	0.2-1.1 mg/dL	4.5 $\pm$ 6.7	1.5
Serum creatinine	0.4-1.4 mg/dL	5.1 $\pm$ 3.0	3.6
Blood urea	15-40 mg/dL	74.3 $\pm$ 77.0	65
Aspartate aminotransferase	5-40 IU/L	110 $\pm$ 83.6	75
Alanine aminotransferase	5-40 IU/L	132 $\pm$ 108.9	90
Alkaline phosphatase	40-129 IU/L	164.6 $\pm$ 56.8	140
Dengue IgM antibodies	<9 Panbio units*	33.6 $\pm$ 13.2	27.0
<i>Leptospira</i> IgM antibodies	<9 Panbio units*	26.0 $\pm$ 12.2	22

*<9 Pan bio units is negative; 9-11 is equivocal; >11 is positive.

Table 2. Results of dengue and *Leptospira* IgM antibodies, treatment and outcome of patients with suspected co-infection

Age	Sex	IgM titers in Panbio units		Clinical signs and symptoms	Treatment	Inpatients	
		Dengue	<i>Leptospira</i>			Days	Outcome
43	F	20.9	29.7	Fever, skin rashes, jaundice, renal failure, thrombocytopenia	Crystalline penicillin, doxycycline, patient dialyzed in view of high creatinine metabolic acidosis	4	Survived
45	M	26.7	22.5	Fever, skin rashes, thrombocytopenia, respiratory distress	Crystalline penicillin, doxycycline, hydrocortisone, platelets transfused	7	Survived
55	F	24.3	28.4	Fever, skin rashes, joint pain, thrombocytopenia, multiorgan involvement	Crystalline penicillin, doxycycline	24	Survived
50	M	41.6	18.8	Fever, skin rashes, renal and hepatic failure, acute respiratory distress syndrome	Crystalline penicillin, doxycycline	9	Survived
23	M	30.4	55.8	Fever, headache, skin rashes, hepatic involvement	Doxycycline	5	Survived
50	M	26.7	18.9	Fever, skin rash, renal and hepatic failure	Crystalline penicillin, Doxycycline Dialyzed in view of high creatinine metabolic acidosis	8	Survived
64	M	51.1	18.9	Fever, skin rash, acute respiratory distress syndrome	Doxycycline, platelets transfused	7	Survived
34	M	57.3	15.6	Fever, skin rash, increased bilirubin liver involvement, diabetes mellitus	Doxycycline	8	Survived
39*	F	23.0	25.1	Fever, skin rash, increased bilirubin liver enzymes	Doxycycline	10	Survived

*One patient was positive for HAV IgM antibodies

illnesses like malaria, dengue and typhoid in an endemic area where all febrile diseases are prevalent. The definitive diagnosis of leptospirosis depends on seroconversion or a four-fold rise in antibody titer or isolation of *Leptospira* from a clinical specimen,⁶ whereas

definitive diagnosis of dengue depends on seroconversion or a four-fold increase in antibody titre.⁷ In the present study, only capture IgM ELISA was done for the laboratory diagnosis of leptospirosis and dengue on a single serum sample. Since it is a retrospective study, we could

not obtain a convalescent serum sample to demonstrate a four-fold rise in antibody titers.

Cross-reactivity is a common problem in serology. *Leptospira* IgM ELISA has been shown to cross-react with hepatitis E and A.¹⁵ Dengue IgM ELISA shows cross-reactivity with other flaviviruses like West Nile virus (WNV), St. Louis encephalitis virus (SLE), Japanese encephalitis virus (JEV) and yellow fever virus (YFV), Zika virus.^{7,16} However, in the present study, out of the 9 cases seropositive for both *Leptospira* and dengue, eight were negative for hepatitis A, B, C and E, and one was positive for Hepatitis A IgM. Zika and other flaviviral infections are not common in our area and we have not tested for the same.¹⁷ However, due to growing globalization, frequent travel and presence of its vector, the *Aedes* mosquito, Zika virus and other flaviviruses need to be kept in mind while interpreting the dengue serological test. Moreover, all these patients' history of febrile illness before the hospitalization was ruled out, as dengue IgM can persist for 2 to 3 months after infection. Thus, based on the IgM serology, other laboratory parameters (Table 1) and clinical diagnosis (Table 2), it may be concluded that these 9 patients had co-infection with dengue and *Leptospira*.

Comparison of mean IgM levels of *Leptospira* (n=119) and dengue (n=382) from mono-infected patients with those of co-infected patients (n=9) using Student's t-test did not reveal statistically significant difference in the IgM levels of these groups (p=0.308 and p=0.938, respectively; p<0.05 is significant). Moreover, no significant association was observed in the clinical signs, symptoms and the laboratory parameters of mono-infected and co-infected patients.

As per Indian guidelines for the diagnosis of leptospirosis, a positive *Leptospira* IgM serology needs to be confirmed with MAT or culture,⁶ which is time-consuming and available only in reference laboratories. Hence, we could not perform the MAT test for the confirmation of leptospirosis. Therefore, for a definitive diagnosis, highly sensitive and specific test like PCR for leptospirosis and RT-PCR for dengue represent the need of the hour. However, PCR

for these infectious diseases is available only in reference centers and high-end laboratories. Hence in resource-poor countries, serology is the only laboratory test available for diagnosis.

Lung involvement with cough, hemoptysis, respiratory failure and pulmonary hemorrhage has been reported in leptospirosis.¹⁸⁻²⁰ Moreover, acute liver failure and renal involvement are also seen in some cases of dengue fever, as reported in literature.²¹⁻²⁵ Thus, it is evident that many times dengue and *Leptospira* show mimicking symptoms and it may be challenging to come to a definitive diagnosis solely on the clinical signs and symptoms. In the present study, clinical signs and symptoms of the 9 patients suspected of co-infection were diverse as shown in Table 2. They had varied features like multiorgan involvement, renal/hepatic involvement, acute respiratory distress syndrome (ARDS) and pulmonary edema. Few cases had severe renal and liver involvement as indicated by elevated direct bilirubin and liver enzymes and increase serum creatinine and blood urea (Table 1).

All these 9 patients showed varied clinical symptoms, hematological and biochemical parameters. This indicates that in co-infected patients the clinical picture is highly variable. The presence of skin rash along with jaundice in a febrile patient may be considered as an indicator of co-infection¹⁰ although it was not a significant finding in our study. Moreover, no significant association was observed in the clinical signs, symptoms and other laboratory parameters of mono-infected and co-infected patients. Hence, serology for IgM antibodies may add some value for the diagnosis/differentiation of leptospirosis/dengue in resource-poor countries. However, antibody detection by serological tests has its limitations of cross-reactivity, thus, these tests are to be interpreted with caution to come to a definitive diagnosis. Specific laboratory test like PCR for both dengue & *Leptospira* need to be performed in endemic areas for early confirmation of infection.

Sero-reactive co-infections with dengue and *Leptospira* have been reported from Mysore (43.3%), Chandigarh (0.9%), Kerala (1.3%), Andhra Pradesh (3.6%) and Tamil Nadu (4%).⁸

^{10,25,26} Other countries from where dengue and *Leptospira* co-infection has been reported include Sri Lanka (2 cases), Thailand (19%), Brazil (single case) Jamaica (5%) and Mexico (12%).²⁷⁻³¹ Even in the present study, co-infection was confirmed by serological test and clinical signs were protean.

All the 9 co-infected patients were treated with antibiotics for leptospirosis. Treatment included crystalline penicillin and doxycycline or doxycycline alone with all the supportive treatment modalities depending on the complexity of organ involvement (Table 2). Co-infected patients with diabetes mellitus, multiorgan involvement leading to acute respiratory distress, hepatic, renal failure and dual infection with viral hepatitis stayed in the hospital for a greater number of days compared to other patients. When there is co-infection, addition of specific antibiotics for the treatment of *Leptospira* infection is mandatory whereas mono-infection with dengue virus requires only supportive treatment. These co-infected patients' (n=9) responses to treatment were found to be good, which is in line with most of the previous studies from India and abroad.²⁷⁻³¹

One patient was seropositive for hepatitis A IgM antibodies apart from being positive for dengue and leptospirosis. A similar case of seropositivity for hepatitis A, dengue and *Leptospira* IgM has been reported from Sri Lanka.¹⁵ Hence the study emphasizes the need for a high index of clinical suspicion for co-infections in tropical countries like ours where acute febrile illness may have multiple etiology.

There are some limitations in our study. It is a retrospective study that included only patients admitted to the hospital. Hence the same conclusion cannot be extrapolated to the outpatient population. Further, our data does not include the occupation, social status of the patients and climatic details, as dengue & *Leptospira* outbreaks occur during monsoon due to stagnant water and breeding of mosquitoes. Moreover, in this study diagnosis of co-infection was based on a serological test (IgM ELISA) and protean clinical presentations of patients. Hence, confirmatory tests like MAT and NAAT would have added extra value to our results.

Key messages

- Leptospirosis and dengue have mimicking clinical signs and symptoms, which coexist in endemic areas.
- Co-infection with *Leptospira* and dengue is very difficult to differentiate with serological test in resource poor countries.
- Leptospirosis needs to be differentiated from dengue as the former can be treated with antibiotics, to reduce mortality.
- Suspected co-infection needs to be confirmed by PCR.

Conclusions

The current study emphasizes the possibility of co-infection (3.2%) with leptospirosis and dengue in this part of the country. In endemic areas if protean symptoms are seen in febrile illness patients, physicians must rule out leptospirosis by confirmatory laboratory tests like ELISA and highly specific and sensitive tests like PCR. If co-infection is suspected, treatment with specific antibiotics for leptospirosis is mandatory along with supportive treatment for dengue infection, keeping in mind the complexity of organ involvement.

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Conflicts of interest: All authors – none to declare.

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Ethical approval: All procedures done in the study were in agreement with the ethical standards of the institutional and/or national research committee. Permission has been taken from Institutional Ethics Committee Kasturba Medical College, Mangalore for the conduct of this study.

Informed consent: Informed consent was waived off by the Institutional Ethics committee, as it is a retrospective study involving only collection of data from hospital and laboratory information system.

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