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Research Article

Dengue and Leptospira Co-Infection

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Abstract

Dengue and *Leptospira* not only share ecological niches, but also manifest with similar clinical presentation. Serologic evidence shows that co-infection by both pathogens is not uncommon in endemic areas. After performing a systematic search, we have here reviewed and analyzed a series of case reports on dengue-*Leptospira* coinfection from around the world.

We observed a positive correlation between bilirubin with hematocrit, and a negative correlation between platelets and hematocrit, and platelets and pulse, as well as between fever and creatinine, during co-infection. Mortality was a variable accounting for data clustering. Differences in age may also play a role in the mortality of co-infection with leptospirosis and dengue

A physician's consideration of the possibility of co-infection, and knowledge of the clinical presentation of when both infections are present, may allow for a rapid diagnosis and an adequate treatment plan that may reduce mortality.

INTRODUCTION

Dengue and Leptospirosis are two important causes of acute febrile illnesses in tropical and subtropical areas. An estimated 96 million cases of Dengue infections worldwide per year manifest clinically [1]. In the Americas, 2.35 million cases of Dengue were reported [2], of which 10,200 cases were diagnosed as severe and caused 1,181 deaths [2]. The incidence of Leptospirosis is close to a million cases per year worldwide, with almost 60,000 deaths [3]. The incidence of leptospirosis is highest in tropical and subtropical areas, particularly during outbreaks and in high-exposure risk groups [5].

Dengue can present with symptoms that may mimic other diseases such as leptospirosis which may complicate the diagnosis of a patient with acute febrile illness [5]. Dengue has a wide clinical spectrum and, in some cases, it may be difficult to differentiate it from other infections based solely on clinical-epidemiological criteria. Leptospirosis is an infectious febrile disease, that is also difficult to diagnose [6]. The similarity of their symptoms have shown that diagnostic confusion between these diseases may occur in routine clinical practice [7]. To the risk for misdiagnosis, we need to add the occurrence of co-infection, as these pathogens circulate in shared ecological niches [8].

In this study a collection of cases of co-infection with dengue virus and *Leptospira spp*. from around the world were analyzed in order to determine a clinical marker of severity or mortality.

MATERIAL AND METHODS

Literature search strategy

Literature search strategy comprised of a search on main data bases such as PubMed, EMBASE, and Google Scholar for case reports that included co-infection with dengue and leptospirosis, up to November 2018. Keywords used were lepto AND dengue, dengue fever AND lepto, dengue* AND lepto*, and DENV AND lepto*. No filters were used when using the databases. Case reports were picked based on the following guidelines, inclusion of a patient with diagnosed Dengue and *Leptospira spp*. co-infection and laboratory values reported for that patient. Case reports were excluded if they did not have a diagnosed case of Dengue and Leptospira spp. co-infection or if they did not provide patient information such as laboratory values or symptoms.

Data Retrieval and analysis

Case reports and research articles of co-infection with Dengue and *Leptospira spp.* were thoroughly analyzed by identifying all possible variables related to clinical presentation and laboratory results. Several variables were identified, including markers for clinical severity or mortality of co-infection with Dengue and *Leptospira spp.* Variables presented in the form of symptoms, physical exam findings, and laboratory results, including blood work and serology (Suppl Table 1). Only variables that were in sufficient number (i.e. ≥5) were utilized for further analysis.

Statistical analysis

Whenever variables were in sufficient number (i.e. ≥5) they were included into a XY matrix to perform a correlation analysis, measuring a Pearson or Spearman correlation coefficient, if the data followed a Gaussian distribution or not. Tests for normality included D'Agostino, Shapiro-Wilk, and KS normality tests. The variables that were cross-analyzed were days with fever, bilirubin, ALT, AST, Creatinine, hematocrit, pulse, and platelets. In addition, a heat map showing correlation between the different variables was constructed using Morpheus (Broad Institute, MA).

To analyze mortality 2x2 tables were created to find a statistical significance between age, >25y/o and <25y/o, gender and death or survival. Data for each table was analyzed using a Fischer-exact test and a p-value was obtained. Calculations were done using GraphPad 7.0 software. A principal component analysis (PCA) was performed aiming to observe patterns in the data set containing the multiple variables listed in Table 1. A PCA plot was generated using R software [9].

RESULTS

Search strategy yielded a total of 13 studies included for analysis (Suppl. Figure 1). A table summarizing the demographic characteristics of these cases is presented in Table 1. Supplementary Table 1 shows the variables analyzed across the reported cases. Several variables were observed to correlate with each other. A heat map showing correlation between the different variables is displayed in Figure 1A. Those that presented with a high correlation coefficient and statistical significance are presented in Figure 1 B-D. When using fever as the X value, correlation analysis compared the correlation between AST vs. bilirubin, and pulse vs. platelets. The analysis between hematocrit vs. platelets showed a strong negative correlation (Spearman coefficient -0.810, p = 0.02) (Figure 1B). This negative correlation showed that as platelets numbers decreased, hematocrit increased. When analyzing platelets vs. pulse, the analysis displayed a strong negative correlation (Spearman -0.746, p = 0.027) (Figure 1C). The negative correlation displays that as pulse increases, the number of platelets decreases. Analysis on hematocrit vs. bilirubin displayed a strong positive correlation (Pearson 0.831, p=0.020), indicating that as bilirubin increases, hematocrit also increases (Figure 1D). Using bilirubin as the X value, a correlation analysis of pulse vs platelets displayed a strong negative correlation of (Pearson -0.735, p = 0.030). Using ALT or AST as the X value, a strong positive correlation was observed when analyzing platelets vs. pulse (Spearman -0.810, p = 0.011). When using ALT as the X value, a Spearman correlation was done to analyze fever and creatinine. The data showed a moderate negative correlation (-0.521, p = 0.035).

Two contingency tables were built to analyze joint distribution between age, gender and death. Table 2 displays the analysis between age (<20y/o and >20y/o) and the outcome of death or survival. Given the small numbers, a Fisher's exact test was performed, with statistical significance in death/survival between these two age groups (p = 0.04). When performing the analysis between gender vs. outcome (death or survival) (Table 3), no statistical significant difference was found.

A PCA on the data set containing the multiple variables listed in Table 1, revealed clustering of data with mortality as a variable accounting for clustering towards positive direction of PC2 (eigen values for PC1 and PC2, 1.51 and 1.09 respectively). A PCA plot showing clustering by mortality is shown in Figure 2.

DISCUSSION

As both Dengue and *Leptospira spp.* share ecological niches in the tropics, clinicians need to be aware of the possibility of co-infection, especially in areas of endemicity [5,10,11]. Co-infection of dengue with leptospirosis can sometimes be overlooked due to their similar clinical presentations [5].

Immunological markers could help differentiate the two infections [12], but these are not routinely performed and would certainly be costly. Markers for severity or mortality dependent on antigen-based serologic testing or nucleic detection for both Dengue and *Leptospira spp.* are also costly and time consuming [13]. A timely clinical suspicion for either infection, or for coinfection, is of the essence. A rapid confirmation of leptospirosis would lead into prompt antibiotic treatment, while confirmation of dengue fever would lead to close platelet count monitoring and initiation of supportive measures.

Table 1: A principal component analysis (PCA) was performed aiming to observe patterns in the data set containing the multiple variables.

Country	Year	Author	Sex	Age	Death
India (30)	2002	Kaur	Female	15	No
Oman (31)	2008	Mohammad	Male	41	No
Brazil (16)	2010	Meguins	Male	41	No
France (24)	2012	Cadelis	Female	46	Yes
Puerto Rico (26)	2012	Sharp	Male	42	Yes
India (22)	2013	Singh	Male	40	Yes
Malaysia (32)	2013	Yong	Male	47	No
India (33)	2014	Chopdekar	Male	4	No
			Female	7	No
Puerto Rico (25)	2014	Perez-Rodriguez	Male	22	Yes
			Male	64	Yes
			Male	67	Yes
Sri Lanka (34)	2015	Dandeniya	Male	49	No
Peru (35)	2015	Nunez	Female	10	No
Sri Lanka (15)	2015	Wijesinghe	Male	52	Yes
India (27)	2016	Pan	Male	22	Yes
			Male	64	Yes
			Male	67	Yes

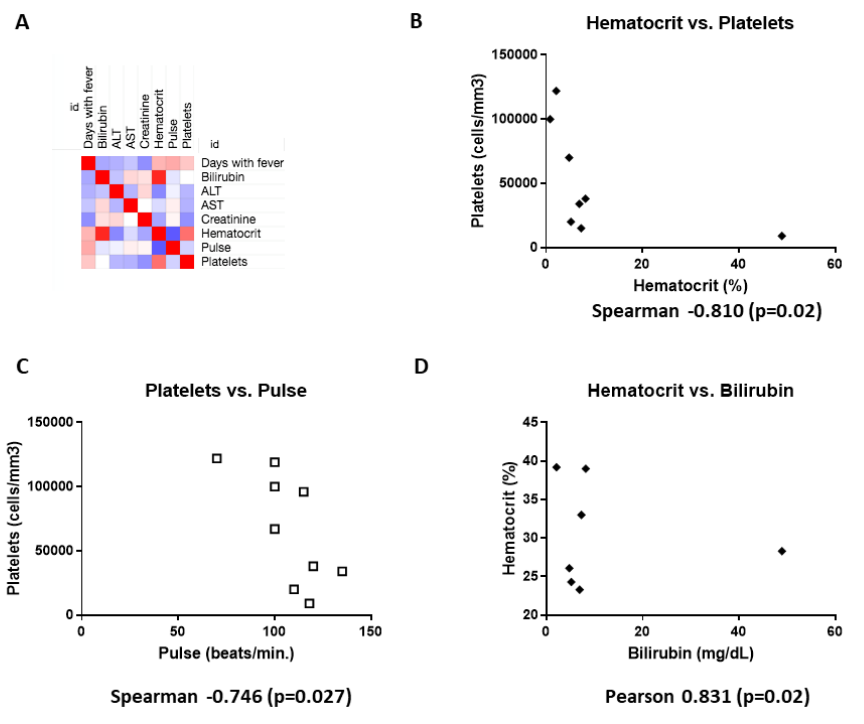

Figure 1 Correlation between main variables in Dengue + Leptospira co-infection cases. A Heatmap showing correlation between the different analyzed variables. B-D Variables that presented a high correlation coefficient and statistical significance.

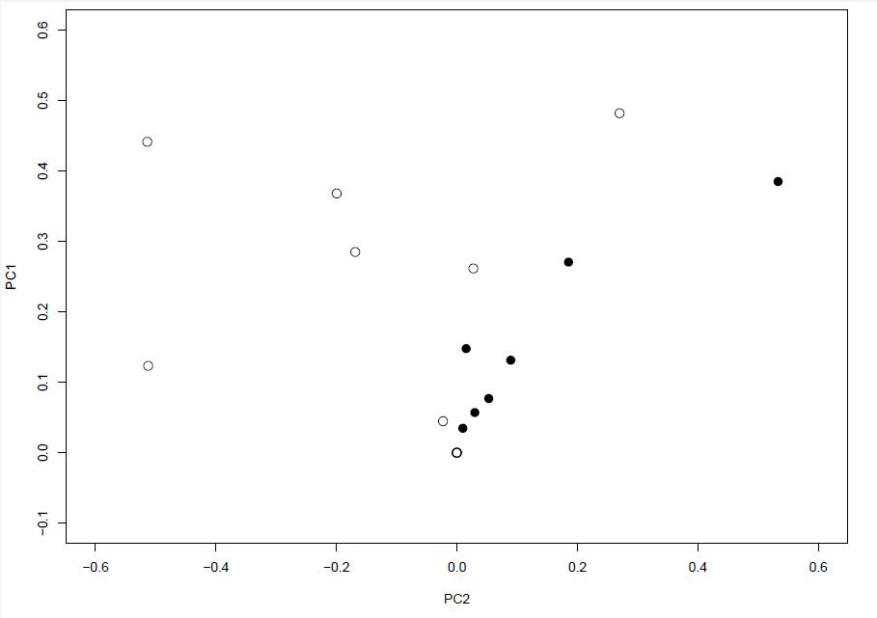

Figure 2 Principal component analysis (PCA) plot showing clustering for mortality amongst analyzed cases. Filled circles (○) represent dead cases, while open circles (●) represent those who survived.

A prospective study in 100 cases of dengue and 100 cases of leptospirosis, found oliguria, icterus, muscle tenderness, anemia, leukocytopenia, thrombocytopenia, elevated erythrocyte sedimentation rate (ESR), acute renal failure (ARF) and hypoalbuminemia to be more commonly in leptospirosis in comparison to dengue (14). ARF, hyperbilirubinaemia, acute respiratory distress syndrome (ARDS), creatine kinase (CK) elevation and thrombocytopenia were predictors of death in leptospirosis, while thrombocytopenia, ARDS and ARF predictors of death in dengue. Their predictive model to distinguish between the two infections found leucocytosis, and increased ESR, creatinine, bilirubin, CK, and decreased albumin to be more

Table 2: Displays the analysis between age (<20y/o and >20y/o) and the outcome of death or survival.

	Death	Survival
<20y/o	0	5
>20y/o	7	6
Fischer's exact test (p = 0.04)		

Table 3: When performing the analysis between gender vs. outcome (death or survival) no statistical significant difference was found.

	Death	Survival
Male	6	7
Female	1	4
Fischer's exact test (p = 0.5)		

indicative of leptospirosis at presentation compared to dengue [14]. A recent study aiming to identify predictors of dengue-leptospirosis infection, did not find any difference between hematocrit, platelet count, ALT, AST, but observed an increase in creatinine phosphokinase (CPK) in leptospirosis-dengue cases retrospectively [10]. Unfortunately, only two of the case reports review in this study had a value for CPK, one showing enzyme elevation [15], and the other, a normal value [16].

A decline in liver function is a common feature of leptospirosis [17] and dengue fever [18]. Hepatic damage can be due to decrease in perfusion occurring in patients with dengue or leptospirosis [19]. The decrease in blood volume will also lead to an increased hematocrit level [19], which is evident with the strong positive correlation we found between hematocrit and bilirubin or thrombocytopenia. Hepatic inflammation may translate clinically in symptoms like nausea, vomiting, or diarrhea, observed in leptospirosis with dengue fever or its more severe presentation, dengue hemorrhagic fever (DHF) [11].

Vascular damage [17], which encompasses endothelial damage and surrounding inflammation, is also a common feature of leptospirosis and dengue [20]. This leads to plasma leakage, a phenomenon in leptospirosis and DHF [11,12]. DHF features plasma leakage and severe bleeding [18]. The decrease in platelet count leads to increased bleeding which in turn increases the risk of the patient developing shock. As our data indicated, thrombocytopenia is associated with an increase in pulse, indicative of the hemodynamic instability occurring in DHF [21] (Suppl. Figure 2). Our findings point out that Leptospira-dengue co-infected cases are more severe cases, possible due to a synergistic effect of the inflammatory mediators induced in the host the presence of both pathogens [20,21].

Intracranial hemorrhage was the main presentation of one of the cases of coinfection with leptospirosis and dengue [22]. Bleeding in the lung, occurs at the alveolar level in leptospirosis [17,23]. Although alveolar hemorrhage is well described in some of the coinfection reports analyzed [15,24], it can only be inferred from the radiologic description of some others [25-27], thus limiting our analysis.

Mortality, as a variable, clustered the data, as observed from the PCA output. Our mortality analysis also showed that an outcome of death due to leptospirosis-dengue coinfection was higher in younger individuals. It could be that a stronger immune response occurring in younger patients leads to a cytokine storm [28] that translates into a more severe disease (29) with a poorer prognosis.

Despite the fact that dengue and *Leptospira* infection can both present with similar symptoms and laboratory findings which can contribute to a difficult diagnosis, our findings are suggestive that some of these biomarkers co-regulate between each other, accentuating their damage, especially in younger patients. Education and awareness of these variables by physicians in endemic areas for both diseases is imperative for close and rapid monitoring and treatment.

CONCLUSIONS

After analyzing the series of cases of dengue and leptospirosis reported around the world, we observed a positive correlation between bilirubin with hematocrit, and a negative correlation between platelets and hematocrit, and platelets and pulse, as well as between fever and creatinine, during co-infection. Mortality was a variable accounting for data clustering. Differences in age may also play a role in the mortality of co-infection with leptospirosis and dengue

A physician's consideration of the possibility of co-infection, and knowledge of the clinical presentation of when both infections are present, may allow for a rapid diagnosis and an adequate treatment plan that may reduce mortality.

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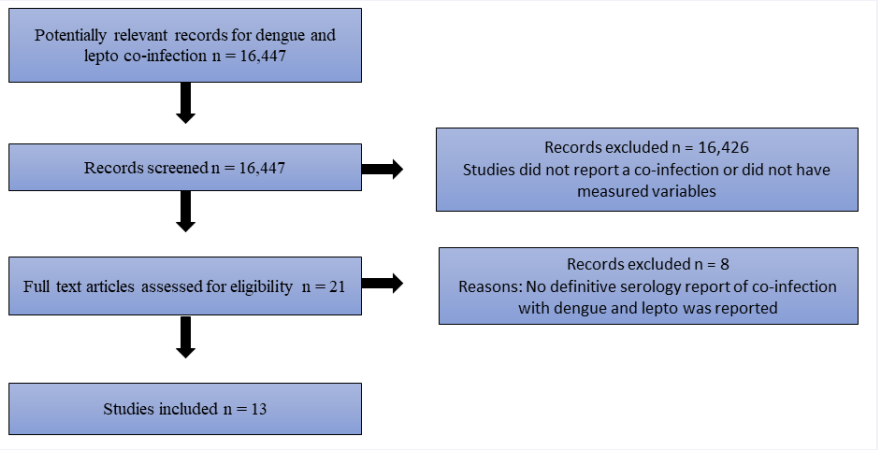

Figure 1s Number of articles searched and retrieved.

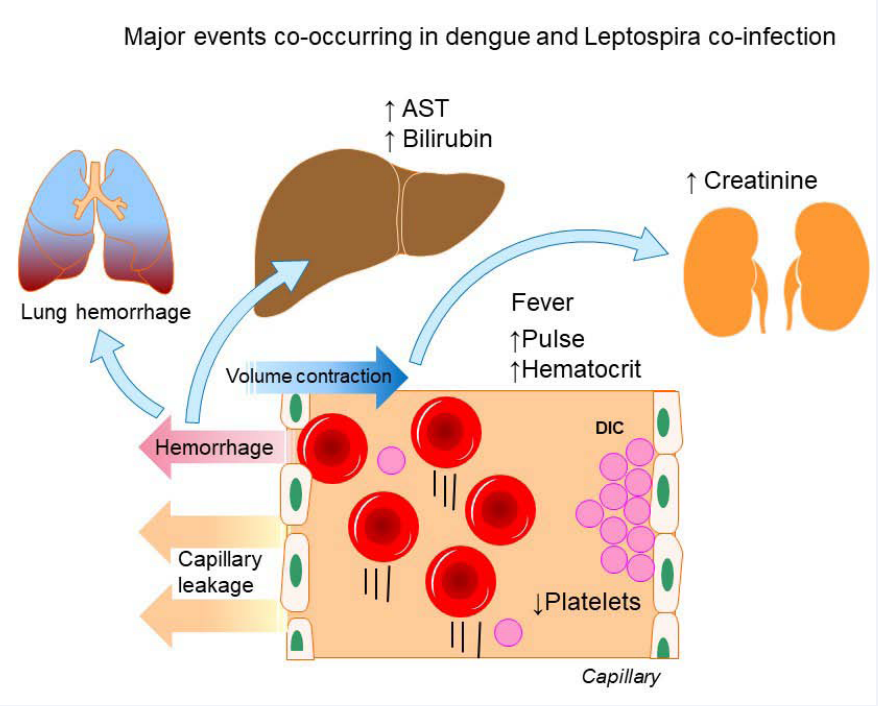

Figure 2s Pathogenesis model of major events occurring in dengue-Leptospira co-infection.

Suppl. Table 1: Variables presented in the form of symptoms, physical exam findings, and laboratory results, including blood work and serology.

Country	Year	Author	Days with Fever	Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)	Hematocrit (%)	Pulse (bpm)	Platelets (cells/mm^3)
India (30)	2002	Kaur	5	1.2	280	135				
Oman (31)	2008	Mohammad	3	2.1	116		7.04		70	122,000
Brazil (16)	2010	Meguins	5		521	1432				119,000
France (24)	2012	Cadelis		0.85	129	184	10.1		100	100,000
Puerto Rico (26)	2012	Sharp	6	4.77	140	285	2.86	26.1		70,000
India (22)	2013	Singh	5	8.2	342	230	6.2	39	120	38,000
Malaysia (32)	2013	Yong	6		55		1.14	39	100	67,000

India (33)	2014	Chopdekar	8					31.3		15,000
			5							53,000
Puerto Rico (25)	2014	Perez-Rodriguez	3	6.9	68	389	1.55	23.3	135	34,000
			2	5.19	351	1117	7.4	24.3	110	20,000
			4	7.28	93	196	6.2	33		15,000
Sri Lanka (34)	2015	Dandeniya	5		103	39	1.65			77,000
Peru (35)	2015	Nunez	5		40	67	0.89	28	115	96,000
Sri Lanka (15)	2015	Wijesinghe	4	48.9	92	126	4.82	28.3	118	9,000
India (27)	2016	Pan	10	5.8						
			10	2.6	104	127	1.3			
			17	4	35		1.9			

ALT: Alanine Transaminase
AST: Aspartate Transaminase