

Case report

Co-infections due to leptospira, dengue and hepatitis E: a diagnostic challenge

Bijayini Behera¹, Rama Chaudhry¹, Anubhav Pandey¹, Anant Mohan², Lalit Dar¹, Martha M Premlatha¹, Ekta Gupta¹, Shobha Broor¹, Parveen Aggarwal³

¹Department of Microbiology, All India Institute of Medical Sciences, New Delhi, 110029, India

²Department of Medicine, All India Institute of Medical Sciences, New Delhi, 110029, India

³Department of Emergency Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India

Abstract

A case of mixed infection due to leptospira, dengue and hepatitis E is reported. Similar clinical presentation and simultaneous transmission of these diseases during rainy season can cause substantial misdiagnosis. Serological tests play a mainstay in diagnosis. Early detection by appropriate serological tests and institution of therapy is crucial and life saving.

Keywords: Leptospira; Dengue; Hepatitis E

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Introduction

Leptospirosis is a zoonosis with a worldwide distribution that almost affects 160 mammalian species. Leptospire are spirochetes comprised of two species: pathogenic *Leptospira interrogans* and free-living *Leptospira biflexa*. Leptospirosis is characterized by a broad spectrum of clinical manifestations, varying from self-limiting anicteric illness to severe form (Weil's syndrome) presenting with jaundice, renal dysfunction, hemorrhagic diathesis and high mortality [1]. The true incidence of human leptospirosis in Northern India is not known because of either a lack of awareness on the part of the treating physicians or the lack of diagnostic technique. We have also reported high incidence of leptospirosis in Delhi and its adjoining areas [2]. Dengue, one of the major mosquito-borne arboviral infections of humans has established itself with endemicity in India. The first epidemic of dengue in India occurred in Kolkata in 1963-64 [3] and ever since the epidemiology of dengue virus has been changing. Delhi, situated in the northern part of India, had faced seven outbreaks of dengue virus (DV) infection due to different serotypes since 1967. Dengue illnesses are caused by any of the four serologically related viruses designated as DENV-1, DENV-2, DENV -3 and DENV-4 [4]. Infection with any one of these serotypes mostly causes a mild, self-

limiting febrile illness referred to as classical dengue fever (DF); however, a few cases develop severe, life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The first major epidemic of DHF that occurred in Delhi in the year 1996 was mainly due to DENV-2, and the last epidemic reported in the year 2006 was mainly due to DENV-3, although concurrent infection with different serotypes were also reported [5,6,7]. Hepatitis E virus (HEV) infection is an acute and self-limiting disease that may cause waterborne epidemics, which have occurred in the Indian subcontinent and elsewhere. ELISA is available for detection of Ig M antibodies against HEV and is specific for recent or ongoing infection [8]. The above-mentioned diseases have always been discussed separately. We hereby report a case of mixed infection due to *Leptospira*, dengue and HEV.

Case report

A 23-year-old male presented to the medicine outpatient department with a history of fever for 10 days, jaundice of 7 days and decreased urination for 3 days. There was no rash or bleeding from any site. General examination revealed fever, icterus, facial puffiness, pedal edema and blood pressure (BP) of 180/130mm Hg. Examination of the abdomen showed moderate ascites and on palpation, the liver

was enlarged 4 cm below the right costal margin. The spleen was not palpable. Chest examination revealed right-sided moderate pleural effusion. Based on the history and clinical examination a differential

worsening of renal function, a renal biopsy of the patient was performed that revealed acute tubulo-interstitial nephritis with marked infiltrates of lymphocytes, neutrophils and eosinophils in

Table 1. Microbiological investigations.

Duration of fever / (admission)	Microbiological investigations and interpretation
10 days	Lepto Tek DriDot, Test[leptoTek DriDot: Organon Teknika, Netherlands] negative. Latex agglutination test with a sensitivity of 90% and specificity of 92%. Dengue Ig M capture ELISA (PANBIO) - Positive (13.6 units/mL) sensitivity of 94.7% and specificity of 98.5%. Dengue virus isolation in C6/36 cell line - Negative RT- PCR for pre- M gene of dengue virus - Negative
21 days	<i>Leptospira</i> IgM ELISA (Serion-virion, GmbH, Würzburg, Germany) - Positive (34 units/mL). Sensitivity of 90.5% and a specificity of 96.5% Dengue IgM capture ELISA (PANBIO) Equivocal (9.3 units/mL), falling titer of dengue specific IgM - suggestive of acute infection.
28 days	<i>Leptospira</i> IgM ELISA (Serion-virion GmbH, Würzburg, Germany) - Positive (61 units/mL) Rising titre of leptospira specific IgM antibodies. Ig M anti- HEV [IAgen HEV IgM kit, Adaltis] - Positive

diagnosis of malaria, enteric fever, dengue, leptospirosis and viral hepatitis was considered. Initial investigations revealed deranged liver and renal functions (total bilirubin: 13 mg%, AST: 155 IU, ALT: 761 IU, serum alkaline phosphatase: 213 IU, blood urea: 143 mg%, serum creatinine: 7.8 mg %). Routine hematological investigations including platelet counts were within normal limits. Blood and urine cultures were sterile. Hence a diagnosis of acute hepatorenal syndrome was made and the patient was managed symptomatically. He was given Ceftriaxone 1g daily and diuretics. Further investigations were directed to establish the specific etiology. Peripheral blood smear for malaria parasite and Widal test for enteric fever were negative. HBsAg and anti-HCV antibodies were negative. Rapid test for *Leptospira* IgM antibodies (LeptoTek DriDot, Organon Teknika, Netherlands) was negative. Patient serum was also tested for dengue specific IgM antibodies (Dengue IgM capture ELISA, PanBio, Australia) which came out to be positive. During the period of hospital stay there was progressive deterioration in the condition of the patient. Liver and renal functions were further deranged and the patient had to undergo hemodialysis twice. On strong clinical suspicion of leptospirosis, a repeat serum sample was sent for *Leptospira* serology on day 21 of admission and was positive in both rapid test and ELISA (Serion Verion, GmbH, Würzburg, Germany). In view of significant

interstitium, which was very much consistent with leptospirosis. Considering the patient’s rising bilirubin levels [13mg% (on day 10) - 41mg % (on day 23)] and predominantly conjugated hyperbilirubinaemia, the patient was investigated for hepatitis E. Anti-HEV IgM (EIAgen HEV IgM kit, Adaltis) was positive. The patient was further managed symptomatically and discharged on day 31 of the admission. At the time of discharge, he was asymptomatic and his liver and renal functions had improved considerably.

Discussion

The above-mentioned case is shocking to the treating physician because of several overlapping clinical features of dengue, leptospirosis and hepatitis E. Existence of simultaneous, multiple infections in an individual is a well-acknowledged fact in today’s world as a result of the AIDS pandemic; however such a diagnosis is still uncommon in an immunocompetent individual . To date, only four cases of mixed infection with dengue and leptospirosis have been described [9-11]; however, the concurrent rise of leptospirosis during a dengue outbreak has been reported[12]. The possibility of co-infection with HEV should also be borne in mind, as water is the vehicle of transmission for both HEV and *Leptospira*. Most of the reports available in the literature show mixed infection with two agents, but

here concurrent infection with three agents has further raised a serious concern for the medical fraternity. The under-diagnosis of such cases is very likely due to the overlapping clinical spectrum [13].

Morbidity and mortality are quite high in such cases. Our findings underscore the need for greater awareness of the possibility of mixed infection as well as the need for optimal use of microbiological laboratory services to reach a specific diagnosis.

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Corresponding Author

Prof. Dr. Rama Chaudhry
Department of Microbiology
All India Institute of Medical Sciences, Ansari Nagar New Delhi-110029, India
E-mail: drammach@gmail.com, ramach003@yahoo.com

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