J R Coll Physicians Edinb 2020; 50: 118–23 | doi: 10.4997/JRCPE.2020.208 ORIGINAL RESEARCH PAPER

Epidemiological, clinical and laboratory features of leptospirosis compared to other acute febrile illnesses

Padma Kumar Balasundaram[1], Libu Gnanaseelan Kanakamma[2], Kumari Jayageetha[3], Baraneedaran Selvarajan[4]

Abstract

Background Leptospirosis is a common zoonotic disease. Many waterborne diseases and mosquito-borne diseases are common causes of acute febrile illnesses in the southern Indian state of Kerala posing diagnostic challenges. The objective of this study was to describe the epidemiological, clinical and laboratory features of leptospirosis diagnosed using the modified Faine's criteria (with amendment) compared to other common acute febrile illnesses.

Methods In this prospective study, all consecutive patients with acute febrile illness, headache and myalgia presenting to our tertiary care hospital's single unit from March 2013 to February 2015 were subjected to detailed history taking and thorough clinical examination. Leptospiral immunoglobulin M (IgM) serology was confirmed by RecombiLISA ELISA and modified Faine's criteria were used for diagnosis of leptospirosis. Other diagnoses for acute febrile illnesses were assigned based on clinical and laboratory investigations. Bivariate and regression analysis was carried out to analyse epidemiological, clinical and laboratory parameters of both groups.

Results A total of 389 patients were enrolled, out of which 110 patients had the presumptive diagnosis of leptospirosis. Among the 279 with non-leptospirosis acute febrile illness, dengue (39%) and other viral febrile illnesses (25%) were the most common diagnoses. Regression analysis identified several epidemiological (contact with contaminated animals or water and drinking unboiled water), clinical (conjunctival congestion and muscle tenderness) and laboratory investigations (leucocytosis, neutrophilia, elevated erythrocyte sedimentation rate [ESR] and aspartate aminotransferase) which were helpful in distinguishing leptospirosis from other acute febrile illnesses.

Conclusion Our study suggests that certain epidemiological, clinical and laboratory features in patients with leptospirosis may allow an early diagnosis. Our study also underscores the usefulness of confirming the leptospiral serology by enzyme-linked immunosorbent assay (ELISA) in combination with relevant epidemiological and clinical features in diagnosing leptospirosis using the modified Faine's criteria.

Correspondence to:
Dr Libu Gnanaseelan Kanakamma
Department of Community Medicine, Government Medical College
Thiruvananthapuram
Kerala
India

Email:
drlibu@gmail.com

Keywords: leptospirosis, acute febrile illness, modified Faine's criteria, ELISA

Financial and Competing Interests: No conflicts of interest declared

Introduction

Leptospirosis is one of the most widespread zoonoses globally with higher prevalence in tropical and sub-tropical areas.[1] It is mainly reported during the rainy season from many south-east Asian countries such as India, Indonesia, Sri Lanka, and Thailand. It has also been reported from developed nations such as the USA, France, Japan, and Germany.[2-6] The clinical manifestations are varied and it has no single specific presenting feature, whether in the mild form of the disease or the severe form (Weil's syndrome). Leptospirosis can resemble dengue, and differentiation from acute viral hepatitis is also difficult sometimes, because of the similarity in clinical features.[7,8] Moreover, co-infection can

[1]Professor, Department of Medicine, Government TD Medical College, Alappuzha, Kerala, India; [2]Assistant Professor, Department of Community Medicine, Government Medical College, Thiruvananthapuram, Kerala, India; [3]Retired Associate Professor of Statistics, Department of Community Medicine, Government Medical College, Thiruvananthapuram, Kerala, India; [4]Senior Resident, Department of Medicine, Government TD Medical College, Alappuzha, Kerala, India.

occur with other febrile illnesses such as malaria or dengue, thus creating a challenge in clinical diagnosis.[9–11]

Though it is difficult to state accurately the incidence of leptospirosis in India, various studies have reported that it accounts for up to 12.7% of febrile illness.[12] Due to changes in the ecosystem, agricultural practices, deforestation, urbanisation, and inadequate waste disposal systems in the country, the areas that were previously *Leptospira*-free have also now become endemic.[13]

Leptospirosis is one of the most frequently reported notifiable infectious diseases in Kerala.[14] Kerala is one of the five states located in Southern India with a population of 34 million. It is in the wet tropical geographical zone and receives heavy rains and occasional floods from April to October. During heavy rains, due to contamination of water sources like ponds, rivers, and canals, *Leptospira* can survive for months. Epidemics of leptospirosis during monsoon months have been reported from different parts of Kerala. *Autumnalis*, *Australis* and *Icterohaemorrhagiae* were the common serogroups identified in a study from Kolenchery, central Kerala, confirmed by culture and serological tests.[15] In another study from Calicut in the northern part of Kerala, *Pomona*, *Shermani* and *Canicola* were the common serogroups detected.[16]

Other waterborne diseases in Kerala, such as infective hepatitis, enteric fever and mosquito-borne disease like dengue fever, are also common causes of acute febrile illnesses, posing increasing challenges to public health. The contributory factors for febrile illnesses are many, including rapid urbanisation, shortage of safe drinking water, poor sewage and solid disposal systems, deforestation and replacement of traditional farming practices. Several specific epidemiological factors, such as contaminated environment, include exposure to water possibly contaminated with *Leptospira* (paddy fields/ agricultural fields, domestic sewage, livestock waste, flood water, construction sites, rivers, canals, ditches etc.), exposure to animals (rodents, livestock, domesticated and wild animals), and occupational exposure (farmers, sewage workers, butchers and abattoir workers, veterinarians, inland fishermen), are relevant to leptospirosis.[17]

The objective of this study was to describe epidemiological, clinical and laboratory features of leptospirosis diagnosed on the basis of modified Faine's criteria (with amendment) utilising IgM *Leptospira* alone in the part C compared to other acute febrile illnesses.[17,18]

Methods

This was a descriptive study carried out prospectively at the TD Medical College Hospital, Alappuzha district, which is a tertiary care centre in central Kerala. This district has an area of 1,415 km^2 and a total population of 2,127,789, of which the urban population is 1,148,146. It receives heavy rainfall during May, June, and the first half of July, during which flooding of rivers and canals is common.

From March 2013 to February 2015, consecutive patients aged between 13 and 60 years of age presenting with acute febrile illness of < 7 days, with headache and body pains (myalgia) to either the outpatient clinic of the principal investigator (PKB), or who were hospitalised under the care of PKB, were included. A detailed history was taken for symptoms such as catarrh, abdominal pain, oliguria, and bleeding manifestations. Documentation also covered relevant information about occupation, water contamination, rainfall and exposure to animals.

A thorough clinical examination in particular noted icterus, conjunctival congestion, subconjunctival haemorrhage, skin rashes, oedema, dyspnoea, and muscle tenderness, hepatosplenomegaly, signs of cardiac failure, meningism and any focal neurological deficit.

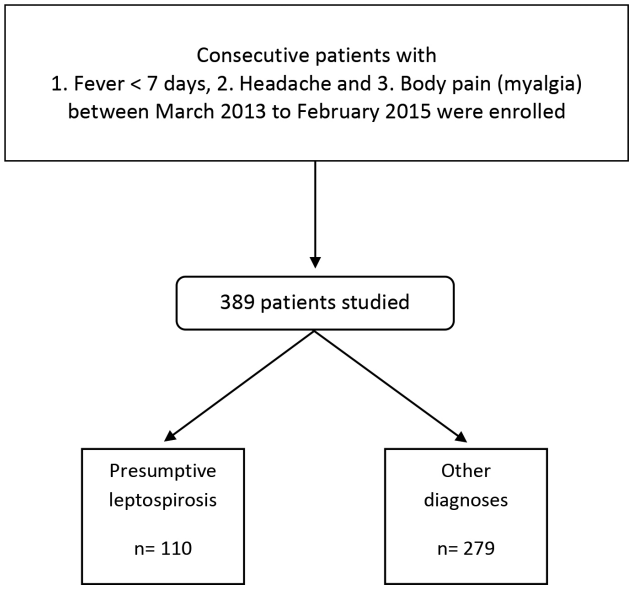
Investigations to identify the cause of acute febrile illnesses were carried out as warranted clinically. This included complete blood count, renal function tests, liver function tests, peripheral blood smear for the malarial parasite, rapid diagnostic test for malaria, IgM serology for dengue and NS1 antigen. Culture of blood was done when enteric fever was suspected, and a urine test for urinary tract infection. A radiograph of the chest was obtained in cases where pneumonia was suspected.

The diagnosis of leptospirosis was made according to the modified Faine's criteria.[17,18] Faine's score was obtained for each patient using clinical (Part A), epidemiological (Part B) and laboratory and bacteriological data (Part C). A score between 20 and 25 makes leptospirosis a possible diagnosis, whereas presumptive diagnosis of leptospirosis is made when the Part A or Part A & Part B score is 26 or more, or the total of Part A, B, C scores is 25 or more. It must be pointed out that the isolation of *Leptospira* in culture makes the diagnosis certain, whereas a polymerase chain reaction (PCR) or a rising titre/seroconversion (in paired sera) in a microscopic agglutination test (MAT) alone gives a score of 25 each.[17,18] However, in the part C criteria we only had access to IgM by ELISA in our institution. This test carries a score of 15 in the aforementioned criteria.[17,18]

IgM antibodies to leptospirosis were tested in the second week of illness, by ELISA using commercial kit RecombiLISA. This kit is a solid-phase ELISA based on the principle of the indirect immunoassay technique for the qualitative detection of IgM anti-*L. interrogans* in human serum or plasma. Antibodies to dengue (IgM) and NS1 antigen were detected by ELISA using a commercial kit.

Statistical analysis was carried out using IBM SPSS Statistics version 25. A bivariate analysis was carried out to assess any significant differences in characteristics of leptospirosis and other acute febrile illnesses. A regression analysis further assessed the data to identify the characteristics which had the most impact in differentiating both groups. Odds ratio with 95% confidence interval was used for finding the strength of association. Variables having p value levels <0.05 were considered as significant.

Figure 1 Consort diagram



The study protocol was approved by the Institutional Ethical Committee of TD Medical College, Alappuzha. (Application No.B3/1573/2010/TDMCA). All study participants gave informed written consent.

Results

During the study period of two years, 389 patients were enrolled, of whom 213 (55%) were female. Of 389, 110 (28%) tested positive for IgM antibodies to leptospirosis by ELISA, and had presumptive diagnosis of leptospirosis based on the modified Faine's criteria (with amendment) (Figure 1).

Of the 110 patients diagnosed as having leptospirosis 62 (56%) were male (Table 1). In this group, the majority of patients i.e. 68 (62%) were between 41 and 60 years of age. Fifty-six (51%) worked in either agriculture or fishing, while 32 were homemakers, 10 were students and 3 were merchants.

Sixty-one patients (55%) gave a history of contact with domestic animals as part of their occupational and recreational activities and 90 (82%) gave a history of contact with contaminated water. Sixty-five patients (59%) used a public water supply, 29 water from a well, and 16 used pond water to bathe. The source of drinking water for 78 (71%) was a piped public water supply and for the remainder it was water from a well. Forty patients (37%) admitted to using unboiled water for drinking.

The most common diagnosis in the non-leptospirosis (other acute febrile illnesses) group was dengue in 108 (39%) patients; these patients were positive for either NS1 antigen or IgM antibodies to dengue (Table 2).

Table 3 compares clinical, epidemiological and laboratory characteristics of leptospirosis versus non-leptospirosis (other acute febrile illnesses) patients. Table 3 also shows clinical and laboratory variables that emerged as significant in bivariate analysis. Epidemiological variables found to be significant in regression analysis were contact with animals, contact with contaminated water, and drinking unboiled water (Table 3). Clinical and laboratory variables found to be significant in regression analysis were conjunctival congestion, muscle tenderness, leukocytosis, neutrophilia, moderate-to-severely elevated ESR, and elevated aspartate aminotransferase (AST).

Discussion

In this study 82% patients with leptospirosis had a history of contact with contaminated water as a part of their domestic and occupational activities. Agricultural workers and homemakers have constant contact with contaminated water which favours entry of *Leptospira* into the body. An epidemiological study in Italy on a waterborne outbreak of leptospirosis underscored that contamination of water with *Leptospira* is an important source of infection.[19] Another study from southern Chile showed that *Leptospira* can survive in the peri-domestic water samples collected from rural households.[20]

In our study, 37% of the patients who developed leptospirosis were using unboiled water for drinking. Consumption of contaminated water may be another source of infection.[2] In a study by the sanitary engineering department of Harvard University it was apparent that all leptospiral organisms were killed in ten minutes or less at 50°C. At a temperature above 60°C, all organisms were killed in less than ten seconds.[21] As *Leptospira* are readily killed by heat, normally cooked food and boiled water are important measures in preventing the infection.

Conjunctival congestion/suffusion was an important clinical feature in 58% of our patients with leptospirosis. WHO also has highlighted conjunctival suffusion as one of the predominant clinical manifestations of leptospirosis.[22] In several studies from India, Brazil, and Hawaii, the presence

Table 1 Demographic and disease-related features of studied patients

Characteristics	Leptospirosis (n= 110)	Other acute febrile illnesses (n=289)
Age; years ±SD	41.29 ±12.08	37.36 ±13.19
Median	44.5	38
Duration of Fever (days)		
Range	7–10	7–14
Mean ± SD	4.84 ± 1.44	4.87 ± 1.63
Median	5	5
Mortality; n (%)	4 (3.6%)	2 (0.7%)

Table 2 Diagnoses of 279 patients with other acute febrile illnesses

Diagnosis	Numbers (%)
Dengue fever	108 (38.70)
Other viral fevers	68 (24.37)
Lower respiratory tract infection	42 (15.05)
Viral hepatitis	35 (12.54)
Acute diarrhoeal disease	12 (4.30)
Enteric fever	5 (1.79)
Upper respiratory tract infection	3 (1.07)
Meningitis	3 (1.07)
Acute pyelonephritis	1 (0.35)
Urinary tract infection	1 (0.35)
Cellulitis of hand	1 (0.35)

of conjunctival congestion was a common finding in leptospirosis.[15,23,24,25] In other febrile illnesses, conjunctival congestion was present only in 10% of the patients, hence it appears to be a useful clinical finding for the early diagnosis of leptospirosis. Therefore, it would be prudent to consider leptospirosis in any patient with non-specific acute febrile illness who has red eyes.[26]

In this study muscle tenderness was present in 83% of the patients with leptospirosis whereas in patients with other febrile illnesses, muscle tenderness was present only in 8%. Muscle tenderness has been reported by many other studies including an Indian study where it was reported in 80% of patients with leptospirosis.[15] Muscle tenderness in the calf and lumbar area are in fact one of the most distinguishing physical findings in leptospirosis.[2]

Leukocytosis is a common feature of leptospirosis. In our study 83% of patients had it and in another study, 70% of patients had leukocytosis.[23] In patients with leptospirosis,

Table 3 Bivariate analysis of epidemiological, clinical and laboratory features in patients with Leptospirosis versus other febrile illnesses

Variables	Leptospirosis n (%)	Other acute febrile illnesses n (%)	Odds ratio OR (95% CI)	P value
Contact with animals *	61(55.5)	27(9.7)	11.62 (6.73–20.07)	0.000
Contact with contaminated water *	90(81.8)	50(17.9)	20.61 (11.62–36.55)	0.000
Drinking unboiled water*	40(36.4)	7(2.5)	22.2 (9.54–51.59)	0.000
Catarrhal symptoms	6 (5.5)	42 (15.1)	0.32 (0.13–0.79)	0.010
Skin rashes	2 (1.8)	47 (16.8)	0.09 (0.02–0.38)	0.00
Abdominal pain	41(37.6)	70(25.1)	1.8 (1.12–2.89)	0.014
Oliguria	12(11)	4(1.4)	8.5 (2.68–26.99)	0.000
Jaundice	40(36.4)	36(12.9)	3.85 (2.29–6.51)	0.000
Conjunctival congestion*	64(58.2)	27(9.7)	12.99 (7.5–22.48)	0.000
Subconjunctival haemorrhage	11(10)	2(0.7)	15.39 (3.35–70.65)	0.000
Oedema	18(16.4)	12(4.3)	4.35 (2.02–9.38)	0.000
Muscle tenderness *	91(82.7)	23(8.2)	53.31 (27.75–102.42)	0.000
Hepatomegaly	43(39.1)	58(20.8)	2.45 (1.51–3.95)	0.001
Tachypnea	78(70.9)	160(57.3)	1.81 (1.13–2.92)	0.013
Leukocytosis (>11000/cmm)*	91(82.7)	42(15.1)	27.03 (14.93–48.92)	0.000
Moderate to severely elevated ESR(>50mm)*	96(87.3)	27(9.7)	64 (32.19–127.21)	0.000
Thrombocytopenia (<100 000/cmm)	69(62.7)	137(49.1)	1.74 (1.11–2.74)	0.015
Neutrophilia (>7700/µl*	73 (66.4)	82(29.4)	4.74 (2.96–7.59)	0.000
Elevated blood urea(>30mg/dl)	60 (54.5)	29(10.4)	10.34 (6.04–17.7)	0.000
Elevated serum creatinine (>1.2 mg/dl)	54 (49.1)	31(11.1)	7.71 (4.55–13.08)	0.000
Elevated serum bilirubin(>1.3 mg/dl)	58 (52.7)	61(21.9)	3.99 (2.49–6.38)	0.000
Elevated AST (>41 U/l)*	102 (92.7)	200(71.7)	5.04 (2.34–10.83)	0.000
Elevated ALT(>38 U/l)	100 (90.9)	187(67)	4.92 (2.45–9.87)	0.000
Elevated alkaline phosphatase(>140 IU/l)	92 (86)	203(73)	2.27 (1.24–4.16)	0.007
Hypoproteinemia(<6.7g/dl)	68 (61.8)	107(38.4)	2.6 (1.65–4.09)	0.000
Hypoalbuminemia (<3.5g/dl)	62 (56.4)	89(31.9)	2.76 (1.75–4.34)	0.000

*Variables that were found to be significant in regression analysis

neutrophilia (66%) was much more common. In a study of children with leptospirosis, leukocytosis with neutrophilia and high absolute neutrophil count was proposed as one of the variables in developing a prediction model for the diagnosis of leptospirosis in children.[27]

In this study, 87% of patients with leptospirosis had moderate-to-marked elevation of ESR. In a comparative study of leptospirosis and viral hepatitis, in patients with leptospirosis, 74% had moderate elevation and 20% had marked elevation of ESR, whereas in patients with viral hepatitis only 35% and 9% had moderate and marked elevation, respectively.[8] In another study, a similar pattern of ESR elevation was seen in all patients with leptospirosis.[28] Anaemia can elevate the ESR by facilitating accelerated sedimentation of erythrocytes through reduction of the number of erythrocytes relative to the volume of plasma and in this study 32% of the patients with leptospirosis also had anaemia.[29]

Hepatic dysfunction is a common manifestation of leptospirosis including elevation of transaminases and serum bilirubin.[23,24] In this study elevation of liver enzymes was seen in more than 90% of patients with slight predominance of AST. Similar slight predominance of AST elevation was also reported in another study.[15] In a comparative study of the paediatric age group mentioned above, elevation of AST was identified as a significant factor to differentiate between leptospirosis and dengue fever in children.[27]

Though our prospective study provides useful information regarding epidemiological and clinical aspects of leptospirosis, it has some limitations. The major limitation is that the diagnosis of leptospirosis was not confirmed either by MAT or PCR. In resource-poor settings such as ours, however, the use of modified Faine's criteria (with amendment) with positive IgM serology confirmed by ELISA, has been validated and allows rapid diagnosis of leptospirosis in the setting of appropriate epidemiological and clinical features.[30]

In conclusion, in this study we have compared epidemiological, clinical and laboratory features of patients with leptospirosis to those with other acute febrile illnesses. Our study has identified certain epidemiological, clinical and laboratory features in patients with leptospirosis which may be useful in making an early diagnosis vis-à-vis other acute febrile illnesses. Though confirmation of leptospiral serology by ELISA is helpful in such scenarios, tests like MAT and PCR remain the gold standard and by using them, future studies may look into developing a prediction model suitable for adults with leptospirosis.

Acknowledgement

The authors would like to thank the Principal, Superintendent and Head of the Department of Internal Medicine, Government TD Medical College, Alappuzha, Kerala, India for their permission to conduct this study.

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