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Age as Prognostic Factor in Leptospirosis

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Abstract

Purpose: To assess the age as prognostic criterion for severity and mortality in leptospirosis.

Methods: We performed retrospective analysis of 100 consecutive leptospirosis cases treated in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2015) (n=100, 90 male, age 37±18 years, urban residents 61%, lethal outcome in 13%), grouped in three age groups – group A (age≤17 years; n1=13), group B (age 18-44 years; n2=55) and group C (age≥45 years; n3=32). Comparative analysis of clinical manifestations, laboratory parameters and outcome was performed. Severity of cases was complexly assessed as mild, moderate and severe and φ-coefficient by modified Pearson's test (interpreted by three-grade score as follows: weak correlation at φ<0.3, moderate 0.31<φ<0.7 and strong – φ≥0.7) was used about correlation with age. Odds ratios (ORs) were calculated.

Results: Mild, moderate and severe cases in group A were 7, 6 and zero, respectively; in group B – 18, 24 and 13 and in group C – 2, 9 and 21. Moderate correlation of severity with age was established in group B (φ=0.53) and strong in group C (φ=0.84). One case in group B and twelve in group C were with lethal outcome (OR 32.4; p<0.0005). The major factors leading to death were lung and brain edema (OR 25.00 and 17.29, respectively) due to severe acute renal failure.

Conclusion: Age over 45 years is associated with severe course of leptospirosis and higher risk for death and requires early intensive treatment.

Keywords: Acute renal failure; Age; Leptospirosis; Outcome

Introduction

Leptospirosis is a widespread zoonosis of global distribution caused by pathogenic spirochetes of the genus *Leptospira*. The infection may be transmitted to humans by exposure to urine of infected mammalian reservoirs, such as peridomiciliary rodents or wild and domestic animals. The clinical spectrum of leptospirosis ranges from asymptomatic or undifferentiated febrile episodes to severe forms. Severe disease is estimated to occur in 5-15% of all human infections, typically presenting as Weil's disease – a triad of jaundice, renal failure, and hemorrhage [1]. The emergence of severe pulmonary hemorrhage syndrome (SPHS) in leptospirosis has recently become of paramount importance, which may present as acute respiratory distress syndrome or massive pulmonary hemorrhage with case fatality higher than 50% in many reports [2]. The presentation of leptospirosis seems to be distinct in different geographic areas worldwide. In Nicaragua and Peru SPHS is uncommon, and presents without classic accompanying features of jaundice and renal failure [2]. In recent years similar observations had reported in Thailand [3,4] and India [5]. In the city of Salvador, Brazil, acute renal failure (ARF) is recognized as the major cause of death with absence of SPHS [2]. A recent systematic review estimated that there are 1.03 (95% CI 0.43 –1.75) million cases of leptospirosis worldwide each year and 58,900 deaths (95% CI 23,800 –95,900) [6,7], which corresponds to an estimated 2.9 million disability-adjusted life years per annum, including 2.8 million years of life lost due to premature death [8].

Worldwide, independent prognostic factors for lethal outcome in leptospirosis have been found to include older age, oliguria, hyperkalemia, abnormal serum creatinine, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, elevated bilirubin, hypotension, arrhythmia, and altered mental status [3,5,9-11]. However, such studies have typically been hospital-, not population-based. Intrinsic virulence variations among serovars have been claimed to partially explain disease severity albeit mild and severe forms may be caused by a broad range of pathogenic serovars [2]. Delay between onset and hospitalization have also been highlighted as determinants of poor outcome.

In Bulgaria, leptospirosis is a reportable disease since 1952, when a database and official registration was initiated. A mean annual incidence rate of 0.9 to 3.1 per 100 000 was reported

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Table 1: Prevalence of the symptoms of leptospirosis.

Symptoms	Whole series (n=100) %	Group A (n_1=13) %	Group B (n_2=55) %	Group C (n_3=32) %	p
Fever	100	100	100	100	=0
Hepatomegaly	92	85	89	100	**<0.01**
Conjunctival suffusions	87	69	96	94	>0.05
Myalgia	86	77	95	75	**<0.025**
Nausea and vomiting	84	85	89	75	>0.05
Splenomegaly	74	46	69	94	**<0.05**
Hepatic dysfunction	71	15	36	81	**<0.005**
Oligo/anuria	69	31	51	78	**<0.005**
Headache	67	92	72	50	**<0.025**
Jaundice	63	31	56	84	**<0.0025**
Tachycardia	54	54	44	75	**<0.0025**
Hypotension	49	31	53	50	**<0.05**
Abdominal pain	41	8	35	66	**<0.0025**
Hemorrhagic diathesis	37	8	27	66	**<0.0005**
Myocarditis	21	0	9	50	**<0.0005**
Meningitis	21	31	22	16	**<0.0025**
Diarrhea	15	0	13	25	>0.05
Cardiac arrhythmias	14	0	7	31	**<0.005**
Acute respiratory failure	14	0	4	38	**<0.0005**
Arthralgia	10	15	11	6	>0.05
Pancreatitis	7	0	5	12	**<0.05**

during the period 1953-1968 followed by decreasing to 0.1 per 100 000 population within next ten years. Since 1976, a mean annual incidence of 0.37 per 100 000 was reported [12], decreasing to 0.18/100 000 (2006-2009) [13]. Because the clinical presentation of leptospirosis varies in different geographic areas, and the fatality rate in severe course is significant, a better understanding of clinical presentation of leptospirosis is needed to enhance its recognition and appropriate treatment. Predictors of lethal outcome must be evaluated in each clinico-epidemiologic setting to consider regional peculiarities [14].

Our objectives were to evaluate the prevalence of the clinical features associated with fatality in severe leptospirosis (in hospitalized patients) in the region of Pleven, Bulgaria, and to assess the age as prognostic criterion for severity and mortality in leptospirosis.

Materials and Methods

We performed retrospective study of all consecutive leptospirosis cases treated after written informed consent in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2015) (n=100, lethal outcome in 13%). A retrospective database for patients presenting with leptospirosis (1976-1984) was initiated and continued prospectively to the December 31st 2015. Subjects were screened by microscopic agglutination test (MAT) for leptospirosis (in the National Reference Laboratory at National Center of Infectious and Parasitic Diseases – Sofia). A positive diagnosis was confirmed if an initial titre of ≥100 for MAT was observed.

The data was obtained through the medical documentation of cases and the protocol included review of medical records, with description of demographic, epidemiologic, clinical, and laboratory information from lethal cases, and survivors. The cases were grouped in three age groups – group A (age≤17 years), group B (age 18-44 years) and group C (age≥45 years) [15]. Comparative analysis of clinical manifestations, laboratory parameters and outcome in three age groups was performed. The data were analysed using the Statgraphics *Plus* Version 2.1. package. We used the t-test and for non-parametric distributions, the χ^2 test; $p<0.05$ was considered to be significant.

Severity of cases was complexly assessed as mild, moderate and severe according to the following definitions [12]:

Mild form of leptospirosis had been defined at mild to moderate intoxication, anicteric or mild icteric, without hemorrhagic diathesis, without involvement of respiratory, cardiac and central nervous system (CNS), with mild renal dysfunction without acute renal failure (ARF).

Moderate form of leptospirosis had been defined at markedly demonstrated intoxication, moderate jaundice, skin hemorrhages, transitory cardiovascular abnormalities without myocardial dysfunction, ARF improving without dialysis.

Severe leptospirosis had been defined at severe intoxication, intensive jaundice with severe hepatic dysfunction, skin hemorrhages and visceral bleeding, toxic myocarditis, severe ARF requiring dialysis, common respiratory and CNS-involvement.

We used φ-coefficient by modified Pearson's test about correlation of severity with age (interpreted by three-grade score as follows: weak correlation at φ<0, 3, moderate 0, 31<φ<0, 7 and strong – φ≥0, 7). Odds ratios (ORs) were calculated.

Results

One hundred patients – mean age 37±18 (8–78) years, 90 males, and urban residents 61%, with leptospirosis were treated in Clinic of Infectious Diseases at University Hospital – Pleven, Bulgaria since January 1st 1976 to December 31st 2015. The mean annual incidence of leptospirosis for 36-year period in Pleven' region was 0.37 per 100 000 population.

The clinical diagnosis of leptospirosis was established before referral to our clinic in 60% of the cases, although exposure to animal excrements after water and animal contacts (57% and 34%, respectively) was certified in 88% of the cases. Summer seasonal predominance (78 cases) was observed – number of cases during June, July, August and September was 12, 25, 29 and 12, respectively.

The age distribution of cases was as follows: group A – age≤17 years old (n_1=13), group B – age 18-44 years old (n_2=55) and group C -age≥45 years (n_3=32).

The prevalence of symptoms in whole series and separately in the

Table 2: Leptospirosis in Pleven region (1976-2015) – laboratory parameters.

Parameter	Reference value	Whole series – mean ± SD (min-max)	Group A – mean ± SD (min-max)	Group B – mean ± SD (min-max)	Group C – mean ± SD (min-max)	p
Hemoglobin (g/L)	120-188	132 ± 20 (65-168)	130 ± 10 (114-147)	132 ± 19 (91-162)	132 ± 22 (65-168)	>0.05
Leucocytes (cells x 10^9/L)	4.0-11.0	13.5 ± 6.5 (2.9-27.6)	9.0 ± 4.2 (2.9-15.3)	12.7 ± 5.8 (4.4-27.6)	15.8 ± 6.6 (2.9-26.4)	**<0.025**
Neutrophils (%)	50-80	81 ± 16 (60-96)	57 ± 14 (60-80)	60 ± 15 (60-96)	65 ± 17 (67-92)	>0.05
Platelets (cells x 10^9/L)	150-400	146 ± 104 (8-445)	177 ± 60 (105-256)	163 ± 109 (18-445)	132 ± 103 (8-437)	>0.05
Urea (mmol/L)	1.7-8.3	22.5 ± 16.9 (2.8-98.6)	11 ± 3.4 (7.8-17.8)	17.5 ± 13.2 (2.8-46.4)	32.8 ± 18.7 (7.8-98.6)	**<0.0005**
Creatinine (μmol/L)	44.2-134	279.7 ± 197 (56-818)	141 ± 67 (88-274)	259 ± 218 (56-818)	349 ± 160 (92-613)	**<0.025**
K^+ (mmol/L)	3.5-5.6	4.1 ± 0.7 (2.6-6.5)	4.3 ± 0.4 (3.7-4.9)	4.0 ± 0.7 (2.6-5.7)	4.1 ± 0.8 (2.7-6.5)	>0.05
Na^+ (mmol/L)	130-151	138 ± 7.1 (112-155)	138 ± 6.3 (126-146)	137 ± 8 (112-155)	138 ± 8 (127-150)	>0.05
Total bilirubin (μmol/L)	3.4-21	157.8 ± 71.5 (3.1-801)	51 ± 38 (7.2-129)	138 ± 73 (3.1-801)	226 ± 174 (7.8-780)	**<0.025**
Direct bilirubin (μmol/L)	0.8-8.5	139 ± 31.7 (2.5-564)	35 ± 24 (7.2-83)	129 ± 34 (2.5-531)	182 ± 131 (7.2-564)	**<0.05**
ASAT (IU/L)	≤37	112 ± 18.5 (6-625)	36.5 ± 17 (12-69)	108 ± 104 (6-490)	150 ± 52 (28-625)	>0.05
ALAT (IU/L)	≤40	96 ± 77.9 (11-382)	34 ± 28 (12-111)	91 ± 62 (14-287)	126 ± 98 (11-382)	**<0.05**
GGT (IU/L)	15-28	168 ± 57.7 (16-568)	72 ± 53 (16-196)	146 ± 57 (27-568)	208 ± 161 (31-523)	**<0.05**
Alkaline phosphatase (IU/L)	50-260	313 ± 237 (37-1431)	261 ± 129 (150-436)	295 ± 215 (51-1099)	346 ± 283 (37-1431)	>0.05
Lactate dehydrogenase (IU/L)	100-360	980 ± 550 (287-2305)	No investigated	887 ± 555 (394-1960)	1062 ± 565 (287-2305)	NA
Creatine kinase (IU/L)	80-190	2508 ± 1948 (68-10438)	No investigated	2275±1042 (68-10438)	2682±1600 (78-8382)	NA
Total protein (g/L)	58-80	64.5 ± 9.2 (47.8-87)	72 ± 6 (64-84.5)	66 ± 8.7 (47.8-87)	60 ± 8.9 (48-78)	**<0.0025**
Albumins (g/L)	35-55	36.2 ± 7.8 (18.5-51)	42.8 ± 7.3 (33.5-51)	39.5 ± 6.4 (27.9-51)	30.2 ± 6.2 (18.5-43.8)	**<0.0005**
Fibrinogen (g/L)	2.0-4.5	6.76 ± 2.39 (1.4-12)	6.8 ± 2.4 (3.9-11.9)	6.7 ± 2.4 (1.4-12)	6.8 ± 2.4 (2.2-10.5)	>0.05
Prothrombin index (%)	80-110	86 ±18 (64-114)	81 ± 14 (61-93)	88 ± 18 (24-112)	85 ± 18 (47-114)	>0.05
Serum amylase (IU/L)	30-300	450 ± 409 (38-2302)	114 ± 25 (97-132)	449 ± 316 (44-2302)	483 ± 432 (38-2265)	>0.05
Hemoglobin (g/L)	120-188	132 ± 20 (65-168)	130 ± 10 (114-147)	132 ± 19 (91-162)	132 ± 22 (65-168)	>0.05
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Serum amylase (IU/L)	30-300	450 ± 409 (38-2302)	114 ± 25 (97-132)	449 ± 316 (44-2302)	483 ± 432 (38-2265)	>0.05

Note: **NA –** not available

age groups is shown on (Table 1).

The comparative analysis of laboratory findings in different age groups revealed significantly higher mean serum levels of urea, creatinine, total/direct bilirubin, total protein and albumins in age group older than 44 years of age ($p<0.05$). These results demonstrate that renal and hepatic functions are affected manifestly in older patients (Table 2).

According to the definitions for mild, moderate and severe leptospirosis mentioned above and after assessment of clinical and laboratory findings showed above, we established the following distribution of cases: mild, moderate and severe cases in group A were 7, 6 and zero, respectively; in group B – 18, 24 and 13 and in group C – 2, 9 and 21, respectively. We used φ-coefficient by modified Pearson's test (interpreted by three-grade score as follows: weak correlation at $\varphi<0.3$, moderate $0.31<\varphi<0.7$ and strong – $\varphi\geq0.7$) about correlation of severity with age. Moderate correlation of severity with age was established in group B ($\varphi=0.53$) and strong in group C ($\varphi=0.84$).

The outcome of treated patients was as follows: 87% of cases survived and were discharged after mean hospital treatment 14.9±7.3 days (from 1 to 46 days) and 13% was with lethal outcome after mean hospital treatment 4.2±2.6 days (from 1 to 10 days). One case in group B and twelve in group C were with lethal outcome (OR 32.4; $p<0.0005$).

The clinical onset of leptospirosis in deceased patients was meanly five days before admission in hospital. All of them had fever, muscular pains, oligo/anuria, two had epistaxis and hemorrhagic rash before admission. Ten deceased patients had co-morbidity including hypertonic disease and chronic alcohol abuse (respectively three cases), past myocardial infarction, stomach ulcer, past tuberculosis (respectively two), podagra and calculous cholecystitis (respectively one). Six of patients with lethal outcome were admitted in other clinical wards (surgery, internal) with different clinical diagnosis – acute pancreatitis, obstructive jaundice and sepsis.

All patients with unfavorable outcome had, besides ARF, at least two other major organ failures. Other abnormalities seen in deceased patients were affected consciousness, multi-site haemorrhagic diathesis (in nine). The major factors leading to death were lung edema and brain edema (OR 25.00; $\varphi=0.659082$ and 17.29; $\varphi=0.527778$, respectively) due to severe ARF.

Pathomorphological investigations were performed in seven deceased cases. Macroscopically, severe lung edema, brain edema leading to cerebellar inclination, multisite bleeding, enlarged congestive liver were established in all of autopsied, pancreatitis in five, peritonitis in one. The histological investigations had demonstrated gastrointestinal and myocardial hemorrhages, focal myocardial necrosis, destruction of liver architectonic, severe tubular necrosis of kidneys in all investigated.

Discussion

Leptospirosis is re-emerging zoonosis with broad clinical spectrum from anicteric and usually self-limiting acute febrile illness to icteric and occasionally fatal form. Icteric leptospirosis is a much more severe disease in which the clinical course is often very rapidly progressive. Severe cases often present late in the course of the disease, and this contributes to the high mortality rate, which ranges between 5 and 15%. Between 5 and 10% of all patients with leptospirosis have icteric form of the disease. The jaundice occurring in leptospirosis is not associated with hepatocellular necrosis, and liver function returns to normal after recovery. Serum bilirubin levels may be high, and many weeks may be required for normalization. There are moderate rises in transaminases levels, and minor elevation of the alkaline phosphatase level usually occurs [1]. It was well demonstrated in our study, that mild to moderately elevated transaminases levels were seen both in whole series and different age groups contrasting to high serum bilirubin levels. Totally 63% of cases were icteric (81% of cases from age group ≥45 years old; $p<0.05$), but hepatic dysfunction was observed in 71%. We had observed severe course in 34% of all cases.

The complications of severe leptospirosis emphasize the multisystemic nature of the disease. Leptospirosis is a common cause of acute renal failure (ARF), which occurs in 16 to 40% of cases. A distinction may be made between patients with prerenal azotemia (non-ARF) and those with ARF. Patients with prerenal azotemia may respond to rehydration, and decisions regarding dialysis can be delayed for up to 72 h [1]. In patients with ARF, oliguria (odds ratio [OR], 9.98) was a significant predictor of death [11]. Risk factors for death in ARF due to acute tubular necrosis have been intensively investigated, but only a few studies have considered these risks when ARF is due to leptospirosis (Weil's disease). ARF due to leptospirosis can be distinguished from acute tubular necrosis because it usually occurs in previously healthy young males and has a high prevalence of hypokalemic and nonoliguric forms [6]. The reported mortality due to leptospirosis varies from 19% in Barbados, 10% in Hawaii, 8% in Trinidad, and 5% in Korea. In the absence of ARF, death due to leptospirosis is very uncommon, but the reported mortality due to leptospirosis with ARF is high: 36% in Barbados, 26% in Sri Lanka [10], and 17% in Turkey [16]. Some factors seem to be related to death in Weil's disease such as age, gender, presence of oliguria, jaundice, and pulmonary involvement [6]. In our study 63% of cases had oliguria (78% of cases from age group ≥45 years old; $p<0.05$). All thirteen deceased patients (13%) had severe ARF, leading to lung edema and brain edema, which were causes for the death. This conclusion was confirmed by patomorphological investigations.

The occurrence of pulmonary symptoms in cases of leptospirosis was first noted by Silverstein [quoted to 1]. Subsequent reports have shown that pulmonary involvement may be the major manifestation of leptospirosis in some clusters of cases and in some sporadic cases. The severity of respiratory disease is unrelated to the presence of jaundice. Patients may present with a spectrum of symptoms, ranging from cough, dyspnea, and hemoptysis (which may be mild or severe) to adult respiratory distress syndrome. Intra-alveolar hemorrhage was detected in the majority of patients, even in the absence of overt

pulmonary symptoms. Pulmonary hemorrhage may be severe enough to cause death [1]. During the past decade, there has been a global increase in recognition of the severe pulmonary form of leptospirosis and Weil's disease with pulmonary involvement. A study from Reunion Island reported the highest rate of pulmonary involvement in leptospirosis (85%) [17]. Spichler A et al. [1], had conducted the largest and most comprehensive population-based study hitherto reported. That analysis does present a reliable understanding of features that predict lethal outcome in severe leptospirosis [2]. In our study we did not observe severe pulmonary form of leptospirosis without ARF. Acute respiratory failure had observed in 14% of cases as a part of multi organ failure (4% of cases from age group 18-44 years old and 83% of cases from age froup ≥45 years old; $p<0.05$).

Cardiac involvement in leptospirosis is common but may be underestimated. Fatal myocarditis was first described in 1935 [quoted in 1]. Clinical evidence of myocardial involvement, including abnormal T-waves, was detected in 10% of 80 severe icteric cases in Louisiana, while similar electrocardiographic (ECG) abnormalities were detected in over 40% of patients in China, India, Sri Lanka, and the Philippines [5,7,10,18], including both icteric and nonicteric cases. The presence of myocarditis was strongly associated with the severity of pulmonary symptoms in anicteric Chinese patients. A mortality rate of 54% was reported in severe leptospirosis cases with myocarditis [18]. Repolarization abnormalities on ECG were considered a poor prognostic indicator (OR 5.9) in severe leptospirosis cases [7], as were arrhythmias (OR 2.83) in a Brazilian series [11]. We had found ECG abnormalities suspected for myocarditis in 21% and cardiac arrhythmias in 14% (in age group ≥45 years old that findings were 50% and 31% respectively; $p<0.05$).

Thrombocytopenia (platelet count of $<100 \times 10^9$/L) occurs in ≥50% of cases and is a significant predictor for the development of ARF. However, thrombocytopenia in leptospirosis is transient and does not result from disseminated intravascular coagulation [1]. Thrombocytopenia as an independent predictor of death has not commonly been observed. Low platelet counts are common in leptospirosis, and human and experimental data have been inconsistent in supporting a role for an underlying disseminated intravascular coagulation process in predisposing to hemorrhagic manifestations in leptospirosis [19]. One potential explanation of thrombocytopenia in leptospirosis is that certain strains of *Leptospira* directly activate platelets; for example, leptospiral proteins that share similarities with human hemostatic factors [2]. We had established thrombocytopenia in 47% of cases despite haemorrhagic diathesis had been observed in 37% (66% of cases from age group ≥45 years old; $p<0.05$). That discrepancy could be explained with prompt intensive and supportive treatment.

Aseptic meningitis may be found in ≤25% of all leptospirosis cases and may account for a significant minority of all causes of aseptic meningitis. Patients with aseptic meningitis have tended to be younger than those with icteric leptospirosis. In their series of 616 cases, Alston and Broom noted that 62% of children ≤14 years old presented with aseptic meningitis, whereas only 31% of patients aged 15 to 29 years did so and only 10% of those over 30 years of age [quoted to 1]. We confirm that fact – aseptic meningitis were found in 21% of all cases and the distribution of cases in the different age groups was as follows: 31% of cases in group ≤17 years old, 22% of cases in group 18-44 years old, and 16% of cases in group ≥45 years old.

Serum amylase levels are often raised significantly in association with ARF, but clinical symptoms of pancreatitis are not a common finding. Necrotizing pancreatitis has been detected on autopsy [1]. Daher E et al. [9], had considered that in all severe cases require attention for pancreatitis [9]. We had observed clinically apparent pancreatitis in 7% of cases (4% with lethal outcome) (12% of cases from age group ≥45 years old; $p<0.05$). One of deceased patients had severe necrotizing pancreatitis that had contribution to sero-fibrinous peritonitis (confirmed on autopsy).

In conclusion, leptospirosis in Pleven region is not common but had presented severe course in 34%. ARF is a leading factor for death and oliguria requires intensive management including dialysis. Patients in older age are with higher risk for severe course and unfavorable outcome and need of referral to a specialized infectious-disease-clinic without delay.

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