Original Article

INVOLVEMENT OF CENTRAL NERVOUS SYSTEM IN LEPTOSPIROSIS

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Summary

Leptospirosis is a worldwide zoonosis with a great importance. The paper aimed to study clinical presentation and laboratory features of leptospiral meningitis and meningoencephalitis. Retrospectively have been studied forty four cases of leptospirosis which have been treated from 1976 to 2009 in Clinic of Infectious Diseases – Pleven. Twenty cases with leptospiral meningitis and meningoencephalitis (group A) have been comparatively analyzed with twenty four cases of leptospirosis without involvement of nervous system (group B). The children and younger ages have been affected more often. Headache, vomiting and neck rigidity have been presented significantly often. Finally neuroleptospirosis have been confirmed by laboratory investigation of cerebrospinal fluid. In conclusion: Involvement of central nervous system in leptospirosis has not been rare. Headache, vomiting and signs for meningeal irritation have been important clinical features but confirmation depends from investigation of cerebrospinal fluid. The early diagnosis and complex treatment are important for favorable outcome.
Key words: leptospirosis, brain edema, meningitis, meningoencephalitis, cerebrospinal fluid

Introduction

Leptospirosis is worldwide zoonosis. Annually in the world 1500 – 2000 cases have been reported but real incidence is higher [1]. This fact is because of diagnostic problems in clinical and laboratory aspects. The disease is with variable combinations of clinical syndromes which provoke diagnostic difficulties with many infectious and non infectious diseases. Diagnostic problems have been presented in neuroleptospirosis. The central nervous system (CNS) in leptospirosis has been affected as aseptic meningitis or encephalitis (more rarely) and peripheral nervous system as neuritis, polyneuritis and polyradiculoneuritis [2, 3, 4]. Other clinical forms of neuroleptospirosis are intracranial hemorrhages, cerebelitis and myelitis [1, 5].

The aim of this research is clinical, laboratory and epidemiological characteristic of leptospiral

meningitis and meningoencephalitis comparing with cases with leptospirosis without CNS involvement.

Materials and Methods

Ninety four cases with leptospirosis have been treated in Clinic of Infectious Diseases at University Hospital – Pleven within thirty four years (1976 to 2009). Twenty patients (21.28%) had been with involvement of CNS (group A; n_1=20) and had been retrospectively compared with twenty four cases without involvement of CNS (group B; n_2=24).

Laboratory parameters have been investigated by conventional laboratory methods and data have been measured in SI units.

T-test (Student) and χ^2-test with significance in $p<0.05$ and odds ratio (OR; significance > 1.000) have been included for statistic analysis.

This study complies with all current international ethic norms.

Results

Sixteen patients with meningitis (17.02% from all leptospiral cases) and four with meningoencephalitis (4.26%) have been observed (ratio 4:1). Eight have been confirmed by microagglutination test (MAT) (Table 1).

Table 1. Serologically confirmed cases with leptospirosis

Serovar	group A		group A	
	cases	%	cases	%
L.tropica	**3**	**15**		
L.tsaratsovo	**3**	**15**		
L.copenhageni	1	5	**10**	**41.67**
L.pomona	1	5	**9**	**37.50**
L .icterohaem.			3	12.50
L.bratislava			1	4.17
L.saxcoebing			1	4.17

L. icterohaem. – L. icterohaemorrhagiae

Mean age in group A is 29.3±13.95 years (9 to 53 years); nineteen male (95%) and one female (Table 2).

Table 2. Age of patients

Age	group A		group A	
	cases	%	cases	%
younger than 18 years	4	20	2	8.33
19-30	8	40	4	16.67
31-40	3	15	6	25.00
41-50	3	15	5	20.83
51-60	2	10	4	16.67
older than 60	-	-	3	12.50

Eleven patients (55%) in group A had been exposed to contaminated water, three with professional risk (15%) and same reported for contacts with rodents (15%). Sixteen from urban and four from rural regions have been registered. Eight cases during July and four during August have been appeared. There are not significant differences in epidemiological data in two groups ($p>0.05$). Acute onset of disease has been registered in all. The symptoms have been compared in Table 3.

Table 3. Clinical symptoms

Symptoms	group A		group B		A
	cases	%	cases	%	
fever	20	100	24	100	>0.05
vomiting	20	100	19	79.17	<0.02
weakness	19	95	21	87.50	>0.05
headache	18	90	14	58.33	<0.02
pains in calves muscles	18	90	21	87.50	>0.05
pains in femoral muscles	15	75	18	75.00	>0.05
darkness of urine	14	70	18	75.00	>0.05
oliguria	13	65	16	66.67	>0.05
generalized myalgia	11	55	14	58.33	>0.05
anorexia	9	45	18	75.00	<0.05
lumbar pains	8	40	15	62.50	>0.05
abdominal pains	7	35	14	5.,33	<0.001
photophobia	4	20	3	12.50	>0.05
hemorrhages	4	20	11	45.83	>0.05
cough	2	10	2	8.33	>0.05
diarrhea	2	10	4	16.67	>0.05
arthralgia	1	5	3	1250	>0.05
hepatomegaly	19	95	23	95.83	>0.05
conjunctival injection	15	75	22	91.67	>0.05
neck rigidity	15	75	2	8.33	<0.025
splenomegaly	11	55	18	75.00	>0.05
tachycardia	8	40	14	58.33	>0.05
hypotension	8	40	9	37.50	>0.05
jaundice	7	35	17	70.83	<0.02
liver tenderness	7	35	9	37.50	>0.05
tachypnea	4	20	2	8.33	>0.05
dyspnea	2	10	1	4.17	>0.05
disorders of heart rhythm	2	10	1	4.17	>0.05
decreased peristalsis	2	10	1	4.17	>0.05
hypertension	2	10	2	8.33	>0.05
rash	1	5	2	833	>0.05

Neurological examination has been demonstrated neck rigidity, Kernig's and Brudzinski's signs in fifteen cases (75%) of group A. Five have been without these symptoms. Patellar and Achilles reflexes have been decreased in eleven (55%) and asymmetric in four (20%). Abdominal reflexes have been suppressed in nine (45%). Reflexes of Babinski's group have been observed in seven (35%). Cranial nerves have been intact. Comma has been registered in four (20%), seizures in three (15%).

In comparative study of symptoms has been found significantly often headache, vomiting and neck rigidity in group A (Table 3) which have been statistically evaluated by t-test, χ^2-test and OR (Table 4).

Table 4. Frequency of the most prevalent symptoms, suggestive for neuroleptospirosis.

Symptom	group A	group A	t-test p	χ^2 p	OR
Headache	18/20	14/24	<0.02	<0.025	6.430
Vomiting	20/20	19/24	<0.02	<0.005	13.570
Neck rigidity	15/20	5/24	<0.025	<0.001	33.000

Investigations of cerebrospinal fluid (CSF) have been revealed slight to moderate increased protein levels in ten cases (50%), ten with normal protein level (mean 0.57 g/L; 0.12-1.42 g/L; SD 0.37). Leucocytes number in CSF has been moderately increased (mean 181.10^6/L; 33-507; SD 144.50) with prevalence of polymorphonuclear cells in ten cases (50%)

(mean 0.48; 0.01-0.88; SD 33.56) and same prevalence of mononuclear cells (mean 0.52; 0.12-0.99; SD 35.12). Glucose level in CSF has been normal in sixteen (80%), decreased in two (10%) and increased in two (10%) %) (mean 3.34 mmol/L; 2.1-9.2; SD 1.51).

Comparative study of laboratory parameters has not revealed significant differences (Table 5).

Table 5. Laboratory investigations

Parameters (SI units)	group A				group B				p
	cases	%	mean	SD	cases	%	mean	SD	
↑Leuc	9	45	12.6	8.16	15	62.50	13.38	7.27	>0.05
↑ESR	16	100	61.88	38.26	22	95.65	61.65	32.28	>0.05
↓Tr	7	63.64	145.27	104.55	14	82.35	114.88	94.52	>0.05
↑T.bil	13	72.22	167.01	106.14	19	86.36	173.95	155.34	>0.05
↑Dir bil	13	72.22	138.72	107.01	18	85.71	137.31	120.35	>0.05
↑ASAT	13	76.47	96.29	60.24	19	86.36	147.23	148.27	>0.05
↑ALAT	14	77.78	85.72	58.46	20	86.96	100.87	58.98	>0.05
↑AP	4	28.57	281.64	183.03	6	35.29	297.88	180.01	>0.05
↑GGT	12	100	162.33	132.90	14	100	149.50	128.64	>0.05
↓TP	3	21.43	64.01	8.24	6	27.27	62.30	9.68	>0.05
↓albumins	4	36.36	39.55	10.92	11	68.75	34.54	7.10	>0.05
↑glucose	8	61.54	7.04	2.47	11	64.71	9.26	6.95	>0.05
↑amylase	5	50.00	334.10	264.62	6	42.86	560.00	646.92	>0.05
↑BUN	10	83.33	23.22	12.29	19	90.48	26.45	15.11	>0.05
↑creatinin	10	83.33	284.5	162.52	18	85.71	338.14	239.14	>0.05
↓Na	3	21.43	139.00	9.26	0	0	136.85	5.41	>0.05
↓Cl	4	44.44	97.67	9.46	3	21.43	98.57	10.89	>0.05
↓K	2	14.29	4.25	0.68	2	10.00	3.96	0.51	>0.05
↑fibrinogen	10	71.43	6.19	2.52	18	85.71	7.06	2.17	>0.05
↓pr. index	2	18.18	91.18	13.64	7	41.18	86.94	13.74	>0.05

↑? above reference. v? below reference. ESR – erythrocytes sedimentation rate. Tr – thrombocytes. T bil. – total serum bilirubin. dir bil – direct serum bilirubin. ASAT – aspartataminotransferase. ALAT – alaninamonotransferase. AP – alkaline phosphatase. GGT – gammaglutamiltransferase. TP – total protein. alb – albumins. BUN – blood urea nitrogen. pr. index – prothrombin index.

Penicillin has been administered in nineteen cases (95%) and Ceftriaxon in one (5%). Methylprednisolon and Dexamethazone have been used in ten (50%); Sol. Mannitoli 10% in all, Furozemid in eleven (55%). Fluids have been infused in all according to concrete needs and disorders in fluid-saline and acid-base balance. In seven cases (35%) plasma, erythrocytes and thrombocytes concentrates and Human Albumin 20% have been transfused. Tree severe cases have been hemodialized.

The course of illness has been moderate in fourteen cases with meningitis (70%); severe in six (30%) – two with meningitis and four with meningoencephalitis. Three with meningoencephalitis have been with lethal outcome. Mortality rate in the present study is 15%. The brain edema, lung edema and hemorrhages are risk factors for death. The mean duration of hospital period is fourteen days (1 to 30; SD 8.69).

Discussion

There have been presented different results in references about incidence of involvement of CNS in leptospirosis. The data have been variable from 4.7% to 80% [4, 6, 7, 8, 9, 10, 11]. In cases with lumbar puncture pathological changes in CSF have been found in 95% in anicteric cases of leptospirosis and in 69.4% in icteric. But real conclusion for incidence of neuroleptospirosis has been defined from investigation of CSF [quoted in 12]. This fact in the present study has been confirmed in five cases with leptospiral meningitis in which there are not clinical signs of

meningeal irritation.

Leptospiral etiology of meningitis has been suggested relatively frequently when the agent has not been isolated [13, 14]. PCR is most sensitive for confirmation – in 39.80% (MAT – in 8.74%; ELISA – in 3.88%) [15, 16].

About significance of concrete serovars *L. canicola, pomona, mitis, bataviae, gryppotyphosa, sejroe, australis B* and *hebdomadis* have been reported (in Bulgaria *L. pomona*) [12]. In the recent years by many researches have been confirmed the role of *L. icterohaemorrhagiae* [7], canicola [17], *sejroe, pomona, australis* [7, 10]. In the present study *L. tropica* and *tsaratsovo* have been the major agents of leptospiral meningitis and meningoencephalitis.

Most cases have been registered during the summer with importance of contaminated water as epidemiologic factor; male have been prevalent. More of cases have been children to eighteen years old (20%) and young adults nineteen to thirty years old (40%); in group without involvement of CNS respectively 8.33% and 16.67%. These data have been correlated with others reports – Alston JM et al. (1958) have been found 62% of cases with leptospiral meningitis in age to fifteen years old, 31% in ages from fifteen to thirty years old and only in 10% older than thirty years [quoted in 7]. Other researches for leptospirosis in children have been found frequent involvement of CNS [3, 6, 8, 9, 13, 17, 18, 19]. As casuistic has been reported case of leptospiral meningitis in 19-month-old male child [20].

The major clinical symptoms are severe headache, vomiting and neck rigidity which have been confirmed in this research. It has been known that in the pathogenesis of involvement of CNS have been presented immunological mechanisms – changes in CSF have been appeared during the second week when leptospira have been disappeared from CSF [10, 12, 21]. More rarely have been observed cases of primary neuroleptospirosis as single localization [1]. Leptospires have been able to persist in aqueous humor and CSF [15] and pathological changes in the meninges and encephalon in these cases have been provoked directly from them, which has been observed post mortem by PCR [22]. Pathomorphological examinations of Matiash VI et al. (1997) have been shown more frequent occurrence of leptospiral meningitis and meningoencephalitis than have been diagnosed clinically [23]. There are cases of neck rigidity without changes in CSF [7, 10, 12].

Slightly or moderately increased protein levels in CSF in 50% of cases have been found in this study; moderately increased numbers of leucocytes with prevalence of neutrophyls in 50% of cases in the onset but in following days monocytes have been prevalent. Glucose levels have been normal in 80%. These data have been correlated with other authorities [7, 10, 12, 21]. In consideration of possible similarity of CSF parameters in zoonotic diseases with other etiology (such as Listeria monocytogenes), diagnostic difficulties appeared in some cases [24]. Epidemiological data and multiorgan disorders were helpful for correct diagnosis.

The early diagnosis and adequate treatment have been significant for favorable outcome. Three patients with leptospiral meningoencephalitis died because of severe brain edema, lung edema and generalized bleeding.

Conclusion

Involvement of CNS in leptospirosis has not been rare. Neuroleptospirosis have been observed more frequent in children and young adults. Headache, vomiting and neck rigidity have been the major clinical symptoms but confirmation depends from investigation of CNS. The early diagnosis and complex treatment are important for favorable outcome.

References

1. Panicker JN, Mammachan R, Jayakumar RV. Primary neuroleptospirosis. Postgrad Med J. 2001;77(911):589-90.
2. Arnaudova Ch, Popivanova N, Vasileva P. Leptospiral neuroinfections. Scientific works of Union of Scientists in Bulgaria – Plovdiv. 2000;1:125-7. (In Bulgarian)
3. Bal AM, Bharadwaj RS, Gita N, Joshi SA, Thakare JP. Guillain-Barre syndrome in a pediatric patient following infection due to Leptospira. Jpn J Infect Dis. 2003;56:29-31.
4. Mathew T, Satishchandra P, Mahadevan A, Nagarathna S, Yasha TC, Chandramukhi A, et al. Neuroleptospirosis – revisited: experience from a tertiary care neurological centre from south India. Indian J Med Res. 2006;124:155-62.

5. Kavitha S, Shastry BA. Leptospirosis with transverse myelitis. J Assoc Physicians India. 2005;53:159-60.
6. Agesilas F, Gey F, Monbrunt A, Combes JC, Llanas B, Schlossmacher P, et al. Acute leptospirosis in children in Reunion Island: a retrospective review of 16 cases. Arch Pediatr. 2005;12:1344-8.
7. Levett PN. Leptospirosis. Clin Microbiol Rev. 2001;14(2):296-326.
8. Marotto PC, Marotto MS, Santos DL, Souza TN, Seguro AC. Outcome of leptospirosis in children. Am J Trop Med Hyg. 1997;56(3):307-10.
9. Rajajee S, Shankar J, Dhattatri L. Pediatric presentations of leptospirosis. Indian J Pediatr. 2002;69(10):851-3.
10. Tappero J, Ashford D, Perkins B. Leptospira species (leptospirosis). In: Mandell G, Bennet JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 5th ed. Philadelphia: Churchill Livingstone; 2000. p.2495-501.
11. Vieira A, Barros MS, Valente C, Trindade L, Faria MJ, Freitas F. Human leptospirosis. A short review concerning a caseload. Acta Med Port. 1999;12(12):331-40.
12. Mitov A, Yankov N. Leptospirosis. Sofiia; MF; 1959. (In Bulgarian)
13. Silva HR, Tanajura GM, Tavares-Neto J, Gomes ML, Linhares AC, Vasconcelos PFC, et al. Aseptic meningitis syndrome due to enterovirus and Leptospira sp in children of Salvador, Bahia. Rev Soc Bras Med Trop. 2002;35(2):159-65.
14. Watt G, Manaloto C, Hayes CG. Central nervous system leptospirosis in the Philippines. Southeast Asian J Trop Med Public Health. 1989;20(2):265-9.
15. Romero EC, Billerbeck AE, Lando VS, Camargo ED, Souza CC, Yasuda PH. Detection of Leptospira DNA in patients with aseptic meningitis by PCR. J Clin Microbiol. 1998; 36(5):1453-5.
16. Silva MV, Camargo ED, Batista L, Vaz AJ, Ferreira AW, Barbosa PR. Application of anti-leptospira ELISA-IgM for the etiologic elucidation of meningitis. Rev Inst Med Trop Sao Paulo. 1996;38(2):153-6.
17. Suarez Hernandez M, Bustelo Aguila J, Perez Gonzalez L, Gorgoy Gonzalez V. Outbreak of leptospirosis, predominantly meningoencephalitic, among children in the municipality of Moron. Rev Cubana Med Trop. 1991;43(2):136-9.
18. Vaptsarov I, Petrov P. Meningitis in benign leptospiral diseases in children. Suvr Med (Sofiia). 1954;5(2):48-65. (In Bulgarian)
19. Karande S, Bhatt M, Kelkar A, Kulkarni M, De A, Varaiya A. An observational study to detect leptospirosis in Mumbai, India, 2000. Arch Dis Child. 2003;88(12):1070-5.
20. de Souza AL, Sztajnbok J, Marques SR, Seguro AC. Leptospirosis-induced meningitis and acute renal failure in a 19-month-old male child. J Med Microbiol. 2006;55:795-7.
21. Bezerra HM, Ataide Junior L, Hinrichsen SL, Travassos FM, Travassos PT, Silva MJ, et al. Involvement of the nervous system in leptospirosis. III. Immunologic reactions in the blood and cerebrospinal fluid. Arq Neuropsiquiatr. 1993;51:469-74.
22. Brown PD, Carrington DG, Gravekamp C, van de Kemp H, Edwards CN, Jones SR, et al. Direct detection of leptospiral material in human postmortem samples. Res Microbiol. 2003;154(8):581-6.
23. Matiash VI, Anisimova IuN. The clinico-morphological characteristics of the nervous system lesions in icterohemorrhagic leptospirosis. Lik Sprava. 1997;3:94-9.
24. Ilieva PK, Tzvetanov P, Atanassova MK. Brainstem encephalitis due to listeria monocytogenes: case report. Bulgarian Neurology, 2006;6(3):147-9. (In Bulgarian)