Trakia Journal of Sciences, Vol. 6, No. 2, Suppl. 3, pp 75-79, 2008

Available online at:
http://www.uni-sz.bg
ISSN 1312-1723

Original Contribution

LEPTOSPIRAL MENINGITIS AND MENINGOENCEPHALITIS

Gancheva G., Ts. Doichinova, P. Ilieva
Department of Infectious Diseases, Epidemiology, Parasitology and Tropical Medicine
Medical University, Pleven, Bulgaria

ABSTRACT

This study has been aimed to clinical, epidemiological and laboratory characteristic for evaluation of diagnostic criteria in leptospiral meningitis and meningoencephalitis. Retrospectively have been studied ninety four cases of leptospirosis which have been treated from 1976 to 2005. Twenty cases with leptospiral meningitis and meningoencephalitis have been comparatively analyzed with twenty four cases without involvement of nervous system. The children and younger ages have been affected more often. Headache, vomiting and signs for meningeal irritation have been confirmed as diagnostic criteria for involving of nervous system. Finally neuroleptospirosis have been confirmed by laboratory investigation of cerebrospinal fluid.
Key words: leptospirosis, brain edema, meningitis, meningoencephalitis, cerebrospinal fluid

Leptospirosis is worldwide zoonosis. Annually in the world 1500 - 2000 cases have been reported but real incidence is higher [15]. 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 poly-radiculoneuritis [1, 5, 13]. Other clinical forms of neuroleptospirosis are intracranial hemorrhages, cerebelitis and myelitis [10, 15].

The aim of this research is clinical, laboratory and epidemiological characteristic of leptospiral meningitis and meningo-encephalitis for confirmation of diagnostic criteria.

Address for correspondence: ***Dr. Galya Gancheva, Department of Infectious Diseases, University Hospital, Georgy Cochev str. 8°, 5 800 Pleven, Bulgaria***
Tel.: +359 064886301; Fax: +359 064886439;
E-mail: galya_gancheva@abv.be

MATERIAL AND METHODS

Ninety four cases with leptospirosis have been treated in Clinic of Infectious Diseases at University Hospital - Pleven within thirty years (1976 to 2005). 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). Statistic analysis include T-test (Student) and χ^2-test with significance in $p<0,05$ and odds ratio (OR; significance > 1,000). Clinical symptoms and syndromes have been analyzed for definition of diagnostic criteria and evaluation of their sensitivity, specificity, positive and negative prognostic and diagnostic values.

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	with involvement of CNS (group A)		without involvement of CNS (group B)	
	number of cases	%	number of cases	%
L.tropica	**3**	**15**		
L.tsaratsovo	**3**	**15**		
L. Copenhagen!	**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

Mean age in group A is 29,3± 13,95 years (9 to 53 years); nineteen male (95%) and one female.

Table 2. Age of cases.

age	with involvement of CNS (group A)		without involvement of CNS (group B)	
	number of cases	%	number of cases	%
below 18 y.	**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	група A (n_1=20)		група B (n_2=24)		p
	болни бр.	%	болни бр.	%	
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*	*58,33*	*<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	12,50	>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**
I 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**	**8,33**	**>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 signs of irritation of meninges in group A (Table 3) which have been defined as diagnostic criteria for involvement of CNS in leptospirosis (Table 4).

Table 4. Diagnostic criteria for involvement of CNS in leptospirosis.

symptom	Group A	group B	t-тест p	z^2 p	OR	sensitivity %	specificity %	positiveprog. value	negative progn. value	diagn. 1 value 1
headache	18/20	14/24	<0,02	<0,025	6,43	90	41,67	56,25	83,33	63,64
vomiting	20/20	19/24	<0,02	<0,005	13,57	100	20,83	51,28	100	56,82
meningea 1 irritation	15/20	5/24	<0,025	<0,001	33	75	50	88,24	81,48	84,09 1

Investigations of cerebrospinal fluid (CSF) have been revealed slight to moderate increased protein levels in ten cases (50%), ten with normal protein level (average 0,57 g/L; 0,12-1,42 g/L; sd 0,37). Leucocytes number in CSF has been moderately increased (av,181.10^6/L; 33-507; sd 144,50) with prevalence of polymorphonuclear cells in ten cases (50%) (av.0,48; 0,01-0,88; sd 33,56) and same prevalence of mononuclear cells (av.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%)%)(av334mmol/L; 2,1-92; sd 1,51). Penicillin has been administered in nineteen cases (95%) and Ceftriaxon in one but eleven patients are with second course (55%). 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 two with meningitis and four with meningoencephalitis. Three with meningo-encephalitis have been with lethal outcome. Mortality rate in the present study is 15%. The brain edema, lung edema and hemorrhages are important 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, quoted in 11, 12, 13, 16, 21, 22]. In group of cases with obligate lumbar puncture pathological changes in CSF have been found in 95% in anicteric cases of leptospirosis and 69,4% in icteric [quoted in 3]. But real conclusion for incidence of neuroleptospirosis has been defined from investigation of CSF [quoted in 3]. This fact in the present study has been

confirmed in five cases with ieptospiral meningitis without clinical signs of meningeal irritation.

Leptospiral etiology of aseptic meningitis has been suggested relatively frequently when the agent has not been isolated [18,23]. PCR is most sensitive for confirmation - in 39,80% (MAT - in 8,74%; ELISA - in 3,88%) [17,19].

About significance of concrete serovars L. canicola, pomona, mitis, bataviae, gryppotyphosa, sejroe, australis B and hebdomadis have been reported (in Bulgaria L. pomona) [3]. In the recent years by many researches have been confirmed the role of L. icterohaemorrhagiae [11], canicola [20], sejroe, pomona, australis [11, 21]. In the present research 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 11]. Other researches for leptospirosis in children have been found frequent involvement of CNS [2, 4, 5, 9, 12, 16, 18, 20]. As casuistic has been reported case of leptospiral meningitis in 19-month-old male child [8].

The major clinical symptoms are severe headache, vomiting and signs for meningeal irritation 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 [3, 6, 21]. More rarely have been observed cases of primary neuroleptospirosis as single localization [15]. Leptospires have been able to persist in aqueous humor and CSF [17] 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 [7]. Pathomorphological examinations of Matiash VI et al. (1997) have been shown more frequent occurrence of leptospiral meningitis and meningoencephalitis than have been diagnosed clinically [14]. There are cases of meningismus [3, 11, 21].

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 [3, 6, 11, 21].

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

In conclusion: Involvement of CNS in leptospirosis has not been rare and is over diagnosed. Neuroleptospirosis have been observed more frequent in children and young adults. Headache, vomiting and signs for meningeal irritation have been important diagnostic criteria but confirmation depends from investigation of CNS. The early diagnosis and complex treatment are important for favorable outcome.

REFERENCES

1. **Arnaudova Ch., Popivanova N., Vasileva P et al. Leptospiral neuroinfections. Scientific works of Union of Scientists in Bulgaria - Plovdiv, 1, 2000, 125-127. Bulgarian.**
2. **Vaptsarov I, Petrov P. Meningitis in benign leptospiral diseases in children. Suvr Med (Sofiia). 1954; 5 (2): 48-65. Bulgarian.**
3. **Mitov A, Yankov N. Leptospirosis. Sofiia, MF, 1959. Bulgarian.**
4. **Agesilas F, Gey F, Monbrunt A, et al. Acute leptospirosis in children in Reunion Island: a retrospective review of 16 cases. Arch Pediatr. 2005 Sep; 12(9): 1344-8. Bulgarian. Bulgarian.**
5. **Bal AM, Bharadwaj RS, Gita N, et al. Guillain-Barre syndrome in a pediatric patient following infection due to Leptospira. Jpn J Infect Dis. 2003 Feb; 56(1):29-31.**
6. **Bezerra HM, Ataide Junior L, Hinrichsen SL, et al. Involvement of the nervous system in leptospirosis. III. Immunologic reactions in the blood and cerebrospinal fluid. Arq Neuropsiquiatr. 1993 Dec; 51(4):469-74.**
7. **Brown PD, Carrington DG, Gravekamp C, et al. Direct detection of leptospiral material in human postmortem samples. Res Microbiol. 2003 Oct; 154(8):581-6.**
8. **de Souza AL, Sztajnbok J, Marques SR, et al. Leptospirosis-induced meningitis and acute renal failure in a 19-month-old male child. J Med Microbiol. 2006 Jun; 55(Pt 6):795-7.**

9. Karande S, Bhatt M, Kelkar A, et al. An observational study to detect leptospirosis in Mumbai, India, 2000. Arch Dis Child. 2003; 88(12): 1070-1075.
10. Kavitha S, Shastry BA. Leptospirosis with transverse myelitis. J Assoc Physicians India, 2005; 53: 159- 160.
11. Levett PN. Leptospirosis. Clin Microbiol Rev. 2001 Apr; 14(2):296-326.
12. Marotto PC, Marotto MS, Santos DL, et al. Outcome of leptospirosis in children. Am J Trop Med Hyg. 1997 Mar; 56(3):307-10.
13. Mathew T, Satishchandra P, Mahadevan A, et al. Neuroleptospirosis - revisited; experience from a tertiary care neurological centre from south India. Indian J Med Res. 2006 Aug; 124: 155-162.
14. Matiash VI, Anisimova IuN. The clinico-morphological characteristics of the nervous system lesions in icterohemorrhagic lepto-spirosis. Lik Sprava. 1997 May-Jun; (3):94-9.
15. Panicker JN, Mammachan R, Jayakumar RV. Primary neuroleptospirosis. Postgrad Med J. 2001 Sep; 77(9 ll):589-90.
16. Rajajee S, Shankar J, Dhattatri L. Pediatric presentations of leptospirosis. Indian J Pediatr. 2002 Oct;69(10):851-3.
17. Romero EC, Billerbeck AE, Lando VS, et al. Detection of Leptospira DNA in patients with aseptic meningitis by PCR. J Clin Microbiol. 1998 May; 36(5): 1453-5.
18. Silva HR, Tanajura GM, Tavares-Neto J, et al. Aseptic meningitis syndrome due to enterovirus and Leptospira sp in children of Salvador, Bahia. Rev Soc Bras Med Trop. 2002 Mar-Apr; 35(2): 159-65.
19. Silva MV, Camargo ED, Batista L, et al. Application of anti-leptospira ELISA-IgM for the etiologic elucidation of meningitis. Rev Inst Med Trop Sao Paulo. 1996 Mar-Apr; 38(2): 153-6.
20. Suarez Hernandez M, Bustelo Aguila J, Perez Gonzalez L, et al. Outbreak of leptospirosis, predominantly meningoencephalitic, among children in the municipality of Moron. Rev Cubana Med Trop. 1991 Apr-Aug; 43(2): 136-9.
21. Tappero J, Ashford D, Perkins B. *Leptospira* Species (Leptospirosis). In: Mandell G, Bennet JE, Dolin R, eds. Mandell, Douglas, and Bennets Principles and Practice of Infectious Diseases, 5th ed. Philadelphia: "Churchill Livingstone", 2000; Vol. 2, Part III, Chapter 229; 2495 - 2501.
22. Vieira A, Barros MS, Valente C, et al. Human leptospirosis. A short review concerning a caseload. Acta Med Port. 1999 Dec; 12(12):331 -40.
23. Watt G, Manaloto C, Hayes CG. Central nervous system leptospirosis in the Philippines. Southeast Asian J Trop Med Public Health. 1989 Jun; 20(2):265-9.