CONCOMITANT INFECTION WITH TICK-BORNE ENCEPHALITIS VIRUS AND BORRELIA BURGDORFERI

J. Cimperman, F. Strle, V. Maraspin-Čarman, S. Lotrič-Furlan, E. Ružič-Sabljić and T. Avšič-Župan

SUMMARY

We hereby describe two patients, one from the south-eastern part and the other from the northern part of Slovenia, where both tick-borne encephalitis (TBE) and Lyme borreliosis are endemic. Both patients showed severe meningoencephalitic signs; one with a two-phase course of disease without a tick bite and the other with a single-phase course of disease with tick bite. High levels of serum antibodies for TBE virus and presence of borrelial antibodies in the serum and in the cerebrospinal fluid were detected, locally synthesized borrelial antibodies in the cerebrospinal fluid were demonstrated as well. After the treatment with ceftriaxone the state of both patients remarkably improved. The first patient complained of intermittent headache, arthralgias and fatigue 6 months after leaving the hospital. The described cases suggest a possibility of a concomitant infections with TBE virus and *B. burgdorferi* in patients living in the endemic areas where Ixodes ticks might be infested with TBE virus and *B. burgdorferi.*

KEY WORDS:

Lyme borreliosis, tick-borne encephalitis, concomitant infection

INTRODUCTION

The causative spirochete of Lyme borreliosis (LB), *B. burgdorferi* and Flavi virus of the ARBO group B are both transferred by the same tick Ixodes ricinus in the same area of Slovenia (1,2,3). LB can affect the skin, joints, heart and the nervous system. Neurologic manifestations may include peripheral neuritis, cranial neuritis, encephalopathy and meningoencephalitis (4,5). Late manifestations of LB can be prevented by appropriate treatment of early infection.

The majority of the subjects infected by tick-borne encephalitis (TBE) virus most probably never develops the disease (3,6). The course of TBE in the Central Europe is milder compared to other areas of the Eastern Europe and Asia (7). Paralysis can be observed in 7% of the patients, death rate is low -

less than 1% (8, 9), No specific treatment is available, but the disease can be prevented by immunization (10).

METHODS

Like all the patients with meningitis admitted to the Clinic of Infectious Diseases Ljubljana, both patients presented in this report underwent the following tests: basic blood tests, urine tests, and routine cerebrospinal fluid (CSF) parameters (concentration of total proteins, glucose and number of cells). Using radial immune diffusion method the concentrations of albumin, IgA, IgG and IgM were measured in both - the serum and the CSF. Borrelial IgM and IgG antibody titers were determined in the serum and CSF with the IFA without absorption (11). B. burgdorferi serotype 2 strain PKo was used as an antigen. Serum antibody titers of 1 : 256 and CSF antibody titers of 1 : 8 were considered as positive.

Intrathecal production of borrelial antibodies was calculated with commonly used formulas (12, 13, 14). Serum TBE virus antibodies were determined with two methods: complement fixation test (CF) using antigen manufactured by BEHRING - 4-fold increase of the titers was considered as significant and enzyme immunoassay (ELISA) manufactured by IMMUNO (IMMUNOZYM FSME - IgG and IMMUNOZYM FSME-IgM) following a two-step "sandwich" system.

Patients were tested for syphilis (VDRL, FTA-ABS). Both patients underwent the ECG and EEG examination.

CASE REPORTS

Case 1: MD, female, 50 yrs

Prior to admission to our clinic the patient enjoyed good health with the exception of mild cervicalgia. During the last three years she was not aware of having been bitten by a tick or an insect, she did not notice erythema migrans (EM). The first signs of disease appeared in the middle of May 1991, with fever up to 38°C, general feeling of discomfort and headache. After 3 days the fever abated the headache disappeared and she was feeling better. 5 days later her condition deteriorated, the fever rose to 39°C, and severe headache and vomiting appeared.

Upon admission to our clinic in the beginning of June 1991 the patient was febrile - 38.6°C, somnolent, with expressed meningeal signs. The results of basic laboratory tests were within normal limits, except ESR which amounted to 30 mm/h, whereas the C-reactive protein (CRP) was negative. Antibody titers in the serum and CSF are demonstrated in the table I. Serologic tests for syphilis were negative. ECG was normal, EEG abnormal with arrhythmic, slow and sharp waves diffusely.

During the first day the patient was treated with analgesics and anti-edematous drugs. On the fifth day ceftriaxone 2 g daily was introduced for 14 days. After two days of antibiotic treatment the patient became afebrile, her psychic state became normal, but severe tremor of the tongue appeared. Within the next 5 days the patient had no headache and her general feeling was improved. She left the hospital after 20 days; tremor of the tongue persisted. At the examination 6 months after leaving the hospital she complained of intermittent headache, arthralgias of the large joints and fatigue. 2 years later EEG was still moderately abnormal with slow activity in the left frontotemporal region.

Borrelial serologic tests performed after leaving hospital remained negative.

Case 2: MF, male, 39 yrs

26 years before admittance to our hospital the patient was treated for osteomyelitis of the left leg.

At the end of May 1993, he was bitten by a tick. There was no EM. In the middle of June 1993 dizziness, overall discomfort, fever up to 40°C, somnolence, tremor and disturbed speech appeared. Headache did not occur.

Upon admission the patient was febrile - 38.5°C, somnolent, with severe tremor of the tongue and hands, bilateral conjunctivitis, and prominent meningeal signs.

Laboratory findings demonstrated increased ESR (37 mm/h), C-reactive protein 23.7 mg/l. Antibody titers of the serum and CSF are shown in the table I. Serologic tests for syphilis were negative.

ECG was within the normal limits, EEG abnormal with sharper activity over the temporal regions, which was more expressed on the right side.

On the third day of hospitalization the patient became excited and disoriented. He was moved to the intensive care unit. An anti-edematous treatment was introduced. On the seventh day the fever dropped, the borrelial serology was positive. Ceftriaxone 2 g i.v. daily was introduced. Within a few days the patient's psychical state improved, and after 14 days of antibiotic .treatment his psychical state was normal.

At examination at the beginning of August 1993

Table 1

	Patient 1		Patient 2	
Parameter	on admittance	4 weeks later	on admittance	4 weeks later
Serum				
Glucose (nmol/l)	4.4		5.3	
Albumin (g/l)	48.2		35.8	
IgM (g/l)	4.52		1.93	
IgG (g/l)	13.4		10.3	
TBE IgG	slightly pos		pos	
(ELISA)	(60VIEU/ml)		(>260VIEU/ml)	
TBE IgM	highly pos		highly pos	
(ELISA)	(OD* 2.871)		(OD* 1.698)	
TBE CF	1:32	1:128	1:8	1:512
BB** IgM				
(IFA)	1:128	neg	1:64	neg
BB IgG				
(IFA)	neg	neg	1:256	1:512
CSF				
Cells (10^6/l)	165		139	
Neutrophils (10^6/l)	11		11	
Lymphocytes (10^6/l)	154		128	
Glucose (mmol/l)	3.4		2.5	
Total proteins (g/l)	0.58		0.73	
IgM (mg/l)	7.25		4	
IgG (mg/l)	60.5		50	
Albumin (mg/l)	329		310	
BBIgM				
(IFA)	1:8		-	
BB IgG				
(IFA)	-		1:32	
BB IgM				
index***	38.99			
BB IgG				
index***			25.75	
Albumin				
quotient****	0.0083		0.0086	

* Optical density
** B. Burgdorferi
*** BB IgG index = TBE tick-borne encephalitis

$$\frac{\text{BB IgG (CSF)}}{\text{IgG (CSF)}} : \frac{\text{BB IgG (serum)}}{\text{IgG (aerum)}}$$

(norm.= 1)

**** Albumin (CSF): Albumin (serum) (norm = 0.0033 - 0.0059)

the patient was feeling well, had no headache, but complained of intermittent pain in the neck.

COMMENT

At least two cases of concomitant infection with TBE virus and *B. burgdorferi* can be found in the literature.

The first report describes a patient in whom a multiple peripheral paresis occurred in the left leg 3 weeks after the onset of neurological symptoms and after recovering from encephalitis (14).

The second report describes a patient who died one month after the disease was noted. The autopsy revealed necrotising encephalitis and myelitis with the involvement of dorsal root ganglion, presumably the main damage was caused by TBE virus (15).

In our cases of concomitant infection, TBE virus infection was verified with highly positive serologic tests for TBE virus. The diagnosis of neuroborreliosis was established on the basis of positive serologic findings in the serum and in CSF, and on the basis of calculated values for borrelial antibodies production in CSF. The beginning of the disease was severe in both patients including meningoencephalitic signs.

TBE virus may cause meningitis or infection of the gray matter of central nervous system (encephalitis and encephalomyelitis) associated with brain edema (16). The course of the disease suggests that the beginning of the disease in the first patient was caused by TBE virus, further disturbances most probably resulted from borrelial infection.

The course of the disease in the second patient suggests that the disease might have been caused by TBE virus or B. burgdorferi. However, the treatment with ceftriaxone resulted in significantly improved state of the patient.

CONCLUSION

In patients with meningoencephalitis coming from the TBE and LB endemic regions the possibility of concomitant infection should be suspected.

REFERENCES

1. Strle F, Cimperman J, Pleterski-Rigler D, Stanek G, Pejovnik-Pusitnek A, Jereb M, Ruzic E. Lyme borelioza u Sloveniji. In: Ropac D, ed. Lyme borelioza u Jugoslaviji. Medicinska akademija Hrvatske, Zagreb 1989: 93-100.

2. Lešničar J. Prispevek h kliniki, epidemiologiji in etiologiji endemskega meningoencefalitisa v Sloveniji. Zdrav Vestn 1955; 24: 66-72.

3. Lešničar J. Dvajset let klopnega meningoencefalitisa na celjskem področju. Celjski zbornik 1973 - 1974: 143-53.

4. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990; 323: 1438-44.

5. Steere AC, Lyme disease. N Engl J Med 1989; 321: 586-96.

6. Matjašič M. Epidemiološko, epizoontološko in laboratorijsko raziskovanje endemičnih žarišč klopnega meningoencefalitisa v SR Sloveniji. (Preučevanje razširjenosti, preprečevanje zoonoz, ki so skupne ljudem in živalim) poročilo o raziskovalnem delu SRS - izvlečki. Ljubljana: Medicinska fakulteta 1979: 206-7.

7. Krausler J. 23 years of TBE in the District of Neukirchen (Austria). Tick-borne encephalitis, Internat Symp Baden/Vienna, Wien, Facultas Verlag 1979: 6-12.

8. Radšel-Medvešček A, Marolt-Gomišček M. Late sequels after tick-borne meningoencephalitis of the patients treated at the University Hospital for Infectious Diseases in Ljubljana during the years 1974 and 1975. Symp. of Arboviruses in the Mediterranean Countries. Brač 1978: 281-84.

9. Radšel-Medvešček A, Marolt-Gomišček M, Clinical characteristics of patients with tick-borne meningo-encephalitis treated at the University Hospital of Infectious Diseases in Ljubljana, Symp. of Arboviruses in the Mediterranean Countries. Brač 1978: 277-80.

10. Kunz C, Heinz F, Hoffmann H. Immunogenicity and reactogenicity of highly purified vaccine against tick-borne encephalitis. J Med Virol 1980: 103-104.

11. Magnarelli LA. Serologic diagnosis of Lyme disease. Ann NY Acad Sci 1988; 593: 154 - 61.

12. Willske B, Schierz G, Preac-Mursic V et al. Intrathecal production of Specific Antibodies against Borrelia burgdorferi in Patients with Lymphocytic

Meningoradiculitis (Bannwarth's Syndrome). J Infect Dis 1986; 153: 304-l4.

l3. Wassmann K, Borg von Zeppelin M, Zimmerman O, Stadler M, Eifert N Thomssen R. Determination of immunoglobulin M antibody against B. burgdorferi to differentiate between acute and past infection. Zbl Bakt 1989, supl 18; 281-89.

14. Kristoferitsch W, Stanek G, Kunz Ch. Doppel-infektion mit Frühsommermeningoencephalitis - (FSME-) Virus und B. Burgdorferi. Dtsch Med Wochenschr 1986; 111: 861-4.

15. Oks J, Viljanen MK, Kalimo H et al. Fatal encephalitis caused by concomitant infection with tick-borne encephalitis virus and B. burgdorferi. Clin Infect Dis 1993; 16: 392-6.

16. Ackermann R, Kräger K, Roggendorf M et al. Die Verbreitung der Frühsommer-Meningoenzephalitis in der Bundesrepublik Deutschland. Dtsch Med Wochenschr 1986; 111: 927-33.

AUTHORS' ADDRESSES

Jože Cimperman, MD, Department of Infections Diseases
University Medical Centre, Japljeva 2, 61000 Ljubljana, Slovenia
Franc Strle, MD, PhD, professor at infectious diseases, same address
Vera Maraspin-Čarman, MD, same address
Stanka Lotrič-Furlan, MD Mr sc, same address
Eva Ružić-Sabljić, MD, Mr Sc, Institute for Microbiology, Zaloška 4
Medical Faculty, 61000 Ljubljana, Slovenia
Tatjana Avšič-Župan, MD, PhD, same address