

Original Article

Tick-borne encephalitis in Serbia: A case series

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Abstract

Introduction: In the Europe, the number of tick-borne encephalitis (TBE) has been increased in the last decade, and the number of endemic areas has been also increased and is still growing. In the present case series, we present clinical and socio-epidemiological data of patients with TBE hospitalized in the period of TBE virus epidemic in Serbia.

Methodology: A case series was conducted in Serbia in 2017. Patients with confirmed TBE were included in the study. Biochemical and serological analysis of blood and CSF, as well as radiological imaging (CT and MRI) were done.

Results: In total, 10 patients with TBE were included in the study. M:F ratio was 1.5:1, while average age was 45.1 years. Half of the patients had severe clinical picture. Endocranial CT scan and MRI did not reveal any abnormality, except in the patient with the most severe CNS infection (meningoencephalomyelitis). Mean value of sedimentation and CRP was slightly elevated (29.6 mm/1hours and 20.1 mg/L, respectively) in 80% of the patients, although elevation was almost negligible. The average number of leucocytes in the cerebrospinal fluid (CSF) was $171 \times 10^6/L$, the mean value of the CSF protein was 1.1g/L. There were no fatal outcomes.

Conclusion: Since other CNS infections have similar clinical picture and CSF finding as TBE, serological analysis for TBE should be included in routine diagnostic practice.

Key words: Tick-borne encephalitis; Serbia; case series; meningitis; encephalitis.

J Infect Dev Ctries 2019; 13(6):510-515. doi:10.3855/jidc.11516

(Received 04 January 2019 – Accepted 24 April 2019)

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Introduction

Tick-borne encephalitis (TBE) is zoonosis, caused by TBE virus (TBEV), a member of the genus *Flavivirus* within the family *Flaviviridae*, causes fatal encephalitis with severe sequelae in humans [1]. TBEV is prevalent over a wide area of the Europe and the number of notified TBE has been increasing the past years despite the increased use of TBEV-vaccine not subsidized by the healthcare system across the Europe [1,2]. TBEV has three genetic and antigenic subtypes: European, Siberian and Far-Eastern. In addition, TBEV has been isolated from dogs, wild rodents and ticks in the area. Ticks belonging to the *Ixodes ricinus* species transmit the European type of the virus, while *Ixodes persulcatus* is a vector of the Siberian and Far East subtypes [2]. In addition to the tick bite, the second most important transmission pathway is the

consumption of fresh milk and dairy products of infected animals, while other transmission pathways are extremely rare [2,3].

Infections caused by European TBEV often have biphasic currents. The first phase is classic viremia, lasts 1-8 days, with the symptoms similar to the flu. The second phase is an asymptomatic period, which usually lasts 1-20 days. After this second phase, about 20-30% people develop a central nervous system (CNS) infection such as meningitis, encephalitis, meningoencephalomyelitis or even meningoencephaloradiculitis [4-7].

The epidemiology of these infections is influenced not only by the intrinsic features of the pathogen, but also by the behaviour and ecology of its vectors and hosts. Temperature, air humidity, access of sunlight, altitude etc. are very important environmental factors

for vector (tick) natural cycle [8]. The season of tick bites and consequently TBE development is usually from April to late October [8-10], when the weather is the most convenient for transmission of this vector-borne disease.

In the present case series we present clinical and socio-epidemiological data of patients with TBE hospitalized in the period of TBEV epidemic.

Methodology

Study design and population

A case series study was conducted in the period 1st June-31st August 2017, in the Department for CNS infections, Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia. Patients with confirmed TBE infection were included in the study. Inclusion criteria were: (i) patients >18 years, (ii) confirmed TBE, (iii) excluded other CNS infection viral, fungal or bacterial and (iv) no presence of other neurological CNS diseases. Written informed consent was obtained from all individual participants included in the study. Ethics committee of Clinical Centre of Serbia approved the study.

Data collection

Patient socio-demographic data, length of hospital stay, previous antimicrobial therapy, laboratory finding and clinical data including presenting symptoms and physical examination were collected.

Laboratory analysis

Patient cerebrospinal fluid (CSF) and blood samples were sent for further analysis for TBEV. A definitive diagnosis was established by obtaining positive specific IgM and IgG antibodies in the serum and CSF, done by enzyme-linked immunosorbent assay (ELISA). In the view of the possibility of other etiology of CNS infection, and especially because of seasonal character of other viruses, other pathogens such as West Nile virus (WNV), Herpes simplex virus 1 (HSV), Varicella zoster virus (VZV), *B. burgdorferi*, *Leptospira* sp. and *Brucella* sp. were excluded by serological analysis from the blood and CSF. In addition, CSF was cultured on conventional bacterial media, and only patients with negative bacterial culture were included in the study.

Biochemical analysis of CSF and blood was done in the term of C-reactive protein (CRP), sedimentation (SE), CSF protein, CSF glucose, leucocytes.

Radiology imaging

Endocranial CT scan of the patients with confirmed TBE was done during first 3 days of hospitalization, with aim to detect any abnormalities. In addition, magnet resonance imaging (MRI) was done, and correlation with clinical finding was done with aim to reveal level and type of TBE (meningitis, encephalitis, meningoencephalomyelitis, meningoencephaloradiculitis).

Statistical analysis

Due to low number of cases (n = 10), only descriptive statistic was performed and categorical variables were summarized by frequencies and percentages. Continuous data were presented as mean \pm standard deviation and counts or percentages (%). All analysis were performed using Statistical Package for Social Science (SPSS) (SPSS version 19.0; SPSS, Chicago, IL, USA).

Results

Sociodemographic data

According to the definition of the TBE case established for 2018 for the European Union [10], 10 patients with TBE were identified, 9 patients had confirmed diseases, while one patient had probably disease. Male to female ratio was 1.5:1, while average age was 45.1 years. Half of the patients (5/10) live in the rural area (suburbs of Belgrade), while only two patients reported previous tick bite prior to the onset of symptoms. Socio-epidemiological data of the patients with TBE are presented in the Table 1.

Clinical picture

Only two patients (20%) had classical biphasic course of the disease. Five patients (50%) had easier clinical picture manifested by meningitis followed by characteristic symptoms and signs (febrile, headache, vomiting, photophobia, and positive meningeal signs), while the average age of these patients was 30 years. On the other hand, the average age of patients with severe clinical picture was higher (53 years). In this group of patients, five patients (100%) had meningoencephalitis, which was manifested by various degrees of consciousness disorder, with other neurological disorders: ataxia (100%), paralyse of the extremity (60%), speech disorder (60%) and tremor (60%). The worst clinical picture had a patient with meningoencephalomyelitis in whom a "poliomyelitis-like" flaccid para-paresis was registered. Socio-epidemiological and clinical data of the patients with TBE are presented in the Table 1.

Radiological findings

Endocranial CT scan of patients with TBE did not reveal any abnormality, except in the patient with the most severe CNS infection (meningoencephalomyelitis) in whom ischemic lesions were detected in the centre of the cerebrum. In addition, MRI of L-S spine segments of this patient revealed arachnoiditis of the cauda equina.

Laboratory analysis

Laboratory analysis revealed leucocytosis in 3/10 patients, while slightly elevated SE (mean value 29.6 mm/h) and CRP (mean value 20.1 mg/L) was observed in majority (80%) of the patients, although elevation was almost negligible. The patient with the most severe clinical picture of meningoencephalomyelitis had the highest value of CRP (77 mg/L). The average number of leucocytes in the cerebrospinal fluid (CSF) was $171 \times 10^6/L$, with predominating lymphocytes in leucocytes formula (85%, mean); the average value of the CSF protein was 1.1 g/L, while CSF glucose values were within the reference values.

Treatment and outcome

Patients with meningitis were treated with symptomatic therapy, while patients with severe CNS infection were treated by antiviral therapy (acyclovir) until negative findings for other viruses (HSV, VZV) were obtained. There were no fatal outcomes; all patients were recovered, except patients with meningoencephalomyelitis/flaccid paraparesis, but also in these patients, significant neurological improvement was achieved during hospitalization.

Discussion

Worldwide, but especially in Europe, the number of TBE has been increased in the recent years, and the number of endemic areas has been also increased and is still growing [10, 11]. It is thought that the number of patients with TBE worldwide has increased by almost 400% in the last 30 years [12]. Possible reasons for this multiple increase are climatic factors, i.e. global warming that leads to an increase in the population of vectors and reservoirs, migration of vectors to higher altitudes, and extended time that people spend outside in parks and gardens [13-15]. Annually, worldwide 10-15.000 cases of TBE are registered, of which 3.000 are in Europe, while endemic are in 27 European countries. At European Union level, TBE is present as endemic seasonal disease in 17 countries [16]. However, a reliable estimation of TBE incidence is not available due to differences in diagnosis, case definitions, and reporting in various endemic countries [15,17].

Given non-specific symptoms, TBE is often undiagnosed and unreported [18]. According to a study by authors from Poland, which represents the endemic region, in 35% of patients with viral meningitis TBEV was confirmed [19], while on the other side in Bulgaria, from 2009 to 2012, from 86 patients with viral meningitis TBEV was confirmed in only three patients [20]. There is no published any epidemiological study on TBE from Serbia. It was not practice in Serbia to do routinely analysis for TBE in the patients hospitalized because of CNS infection. TBEV is specific due to its unstable dynamics and extensive inter-year variations in the number of cases [21], so without comprehensive epidemiological and clinical research, and routine analysis for TBE of every patient with CNS infections,

Table 1. Sociodemographic data and clinical characteristics of the patients with TBE.

No.	Patient	Age	Tick bite	Rural area	SE (mm/h)	Le in blood ($10^9/L$)	CRP in blood (mg/L)	Pleocytosis in CSF ($10^6/L$)	Ly in CSF (%)	Proteins in CSF (g/L)
1	M	40	No	No	30	13.0	10.3	217	91	0.55
2	M	31	No	No	16	7.9	2.7	524	93	1.68
3	M	40	No	No	20	7.0	14.0	85	79	0.36
4	M	39	No	Yes	24	10.7	9.5	390	85	1.40
5	M	41	No	No	22	20.6	12.1	77	71	0.97
6	ME	73	Yes	Yes	50	9.1	33.4	78	69	0.80
7	ME	23	No	No	30	7.3	13.0	131	95	1.83
8	ME	61	No	Yes	44	7.9	8.2	87	76	1.02
9	ME	49	Yes	Yes	10	8.2	2.3	99	88	0.95
10	MEM	60	No	Yes	50	9.3	77.0	26	99	0.90
	Mean	45.7	20%	50%	29.6	10.1	20.1	171.4	85	1.1

M, meningitis; ME, meningoencephalitis; MEM, meningoencephalomyelitis; CRP, C reactive protein; CSF, cerebrospinal fluid; Le, leukocyte; SE, sedimentation; TBE, tick born encephalitis.

the annual number of TBE cases cannot be confirmed. It was confirmed in the previous studies that enzootic hotspots for TBE are located in the northeast of Serbia, around Belgrade [22]. Results of this case series study revealed that the half of the patients with CNS infections live in a rural area, while only two patients reported tick bites before the onset of the first symptoms. The published data indicate that in 30% of cases there is no data on tick bite [3,5,23], and about 1% of people with TBE are considered infected with consuming milk or other products from infected cattle, predominantly goats [24,25].

TBE caused by the European viral subtype has biphasic flow in 2/3 of patients [8], while in the present case series only 2/10 patients had a biphasic course of the disease. The possible explanation could be that mild and non-specific clinical symptoms have not been recognized as the first phase of TBE.

According to other European countries, TBE is commonly presented as meningitis (50%), meningoencephalitis (40%), and meningoencephalomyelitis (10%) [5,8,24,26,27], although research by Stefanoff *et al.* showed that the overall percentage of patients with meningitis in the period 1999-2002 was higher [28]. In the second phase of disease, the clinical spectrum of TBE goes from mild meningitis to severe form of encephalitis with, or without myelitis and spinal paralysis. Neurological symptoms in this stage, in principle, do not differ from other types of acute CNS infections [1,5,29,30], but the severity of the disease correlates with the age [23,30,31]. Our study revealed that the mean age of patients with easier clinical form of disease (meningitis) was lower in relation to the patients with severe clinical form of TBE (meningoencephalitis and meningoencephalomyelitis) (30 years vs. 53 years).

In patients with meningoencephalitis, the most common neurological symptoms are disturbance of consciousness, ataxia, paresthesia of the extremities and cranial nerves, with a typical clinical sign of extremity ataxia [7,27,32]. Paresis occurs in acute phase of TBE in 3-23.5% cases [30]. A "poliomyelitis-like" paralysis occurs because of the involvement of the anterior roots of the spinal cord [26]. In the present study, 50% patients had meningoencephalitis, which was manifested by varying degrees of consciousness disorder, with other neurological symptoms (ataxia, paralysis of the extremities, speech disorder and tremor). The heaviest clinical picture had a patient with meningoencephalomyelitis with a "poliomyelitis-like" flaccid paraparesis.

Pathological findings in endocranial MRI of patients with TBE are found in 15-18%, primarily in the grey matter, extended to spinal cord, pons, cerebellum, basal ganglia and thalamus [7,33,34]. In the present case series, only one patient with severe clinical picture (meningoencephalomyelitis and flaccid paraparesis) had pathological finding of endocranial CT scan (ischemic lesions) while MRI of L-S spine revealed arachnoiditis of the cauda equina. The same pathological findings of endocranial CT and MRI of patients with TBE were already reported by other researchers [35].

Biochemical analysis of blood and CSF of TBE patients are usually non-specific, while elevated inflammatory parameters could be found in the second stage of TBE, primarily elevated SE (90%), CRP (80%) and leucocytosis (75%). CSF analysis usually shows moderately elevated CSF protein and pleocytosis, with prevalence of lymphocytes [1,5,26,31,36,37]. In the present case series leucocytosis was present in 3 patients, while slightly elevated SE and CRP was found in the majority of the patients, what is in accordance with other studies. The patient with the most severe clinical picture had the highest CRP value (77 mg/L). Since the clinical picture and laboratory analysis of blood and CSF are non-specific, the definitive diagnosis of TBE could be confirmed only by serological analysis of blood and CSF [38].

Conclusion

Bearing in mind that other CNS infections are presented with a similar clinical picture and CSF finding as TBE, microbiological (serological) analysis for TBE should be included in routine diagnostic protocols. Long-term epidemiological and clinical studies are needed to identify different environmental factors associated with the emergence and upkeep of enzootic pathogen populations, as well as to identify specific clinical and laboratory parameters related to TBE.

Authors' contributions

JP, AB, SR wrote the manuscript; NK, AU, BM, IM collected patients data; NM, IK, GS critically revised the paper and did language editing.

Ethical standard

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee of Clinical Centre of Serbia approved the study.

Acknowledgements

Dr Aleksandra Barac is funded by the Project of Ministry of Education, Science and Technology of the Republic of Serbia (No. III45005)

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Conflict of interests: No conflict of interests is declared.