Case report

Fatal Case of Imported Tick-Borne Encephalitis in South Serbia

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Abstract: Tick-borne encephalitis (TBE) is vaccine-preventable neglected zoonotic neuroinvasive disease, caused by tick-borne encephalitis virus (TBEV). Many of the Central and Eastern European countries are affected by TBE, which is often poorly perceived by tourists visiting endemic territories. Here we are reporting a fatal case of imported TBE in Serbian resident who was exposed to tick bite during a visit to Switzerland.

Keywords: tick-borne encephalitis; tick; Serbia; Switzerland; fatal

1. Introduction

Tick-borne encephalitis (TBE) is neglected zoonotic neuroinvasive disease, caused by tick-borne encephalitis virus (TBEV), genus Flavivirus, family Flaviviridae [1]. TBEV circulates in natural foci where small mammals act as reservoirs, while hard ticks feeding on them serve as vectors and reservoirs. Most important TBEV vector in Europe is the tick Ixodes ricinus [2]. Humans are accidental hosts of TBEV and infection occurs when exposed during blood meal of infected tick [3], although humans can also get infected by consumption of contaminated milk or non-pasteurized dairy products, causing-small scale epidemics, mostly limited to several households [4].

TBEV foci are complex and dynamic systems requiring specific environment and climate characteristics suitable for the life cycle and/or survival of TBEV vectors and reservoirs, which allow amplification and spreading of the virus. If environmental factors are altered, stable TBEV foci can disappear [5]. In contrast, new foci can emerge if all components are fulfilled and TBEV transmission chain is completed [6,7].

According to phylogenetic clustering and geographical distribution, five main subtypes of TBEV are classified as Western (European, TBEV-Eu), Siberian (Eastern, TBEV-Sib), Far-Eastern (TBEV-Fe), Baikalian (TBEV-Bkl), and Himalayan (TBEV-Him). Although TBEV-Eu is dominant subtype in many European countries, other subtypes (i.e., TBEV-Sib, and TBEV-Fe) can be present in different proportions, especially in Baltic countries and the rest of East Europe [1,3,8].

TBEV endemicity is recognized as specific problem in central European countries (i.e., Slovenia, Slovakia, Czech Republic, Austria and Switzerland), where different recommendations related to preventive immunization against TBE are implemented [3,9].

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Depending on specific country, vaccination against TBEV can be recommended to all residents, or only to specific groups identified as high risk to TBEV exposure. Furthermore, TBE is recognized as disease highly relevant to travel medicine, since tourists visiting endemic territories are under risk of acquiring TBEV infection during activities in rural environment and/or green surface areas after a tick bite or consumption of contaminated milk/dairy product [9,10].

TBE in Serbia is rarely reported and it is most probably highly neglected, given that I. ricinus ticks infected with TBEV were detected in several localities (i.e., Fruška Gora mountain and Belgrade suburban area) [11]. In addition, seroreactivity against TBEV was reported in patients recovered from viral encephalitis of unknown origin [12] and in patients previously infested by ticks [13]. TBEV infection is most often asymptomatic, but occasionally it can manifest as fever-like illness and progress to severe inflammation of the central nervous system (CNS) [3]. Thus, the health practitioners in Serbia are often not able to suspect or recognize TBE in patients with non-specific viral encephalitis, due to absence of uniform case definition on the country level [3,12,13].

Here, we are reporting a fatal case of imported TBE in Serbian resident who was exposed to tick bite during a visit to Switzerland.

2. Case description

On 26 June 2022, 58-year-old male with permanent residency in South Serbia was admitted to local hospital in north-east Switzerland (town St. Gallen; 47.4245°N, 9.3767°E) with quadriparessis, impaired speech, elevated body temperature (up to 38oC), headache, malaise, muscle pain and diarrhea. He was staying in a visit to his family in St. Gallen for 30 days and recalled having a tick bite 14 days ago (09.06.2022.) while hiking in forest area near St. Gallen. He removed the tick by himself using his fingers and discarded it afterwards. He denied existence of any comorbidity, as well as immunization against TBE.

First day of illness occurred approximately seven days after tick bite (16.06.2022.), with development of pain in lower back, headache and malaise and elevation of body temperature. Seven days later, patient started to feel weakness in his upper and lower extremities and experience difficulties in speaking and swallowing. His signs and symptoms progressed until he developed breathing difficulties and was not able to talk, swallow, stand or walk. On 10th day of illness he was admitted to the hospital, where severe right-sided sensory and motor tetraparesis and hyporeflexia were observed. Meningeal signs were absent, while swallowing, corneal and coughing reflexes were preserved. Immediately after hospitalization patient was intubated and mechanically ventilated due to respiratory insufficiency.

Initial laboratory findings (14th day of illness) showed mild blood leukocytosis with lymphopenia and clear cerebrospinal fluid (CSF) with mixed pleocytosis (187 cells/μL: lymphocytes 25%, monocytes 21%), slightly elevated lactate value 2.6 mmol/L (< 2.4 mmol/L), slightly elevated protein level (0.74 g/L, albumin 0.4 g/L) and regular glucose level (3.4 mmol/L). CSF and serum were negative for oligoclonal bands. CSF bacterial culture was negative. Infection caused by herpes simplex virus (1 and 2), varicella-zoster virus, human immunodeficiency virus, SARS-CoV-2 and Borrelia burgdorderi sensu lato complex, as well as existence of autoimmune and paraneoplastic encephalitis were ruled out due to negative laboratory findings. IgM reactive with TBEV antigen were found in

serum and CSF, suggesting flaviviral etiology. Complete list of laboratory examination conducted after admission to the hospital is presented in Table 1.

Parameter of interest	Day of disease			Ref. values
	14	19	27	
Biochemical and hematological analyzes				
Leukocyte count (10^9/L)	11.3	7.5	12.2	4.0-10.0
Neutrophils (%)	86.2	-	78.7	25.0-78.0
Lymphocytes (%)	6.6	-	10.2	20.0-52.0
Creatine kinase (U/L)	496	-	-	<170

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C-reactive protein (mg/L)	7	-	6.4	<8
Glucose (mmol/L)	6.1	-	7.9	3.9-5.6
Aspartate aminotransferase (U/L)	41	413	-	<55
Alanine aminotransferase (U/L)	16	557	429	<55
Gamma glutamyl transferase (U/L)	55	1025	-	<65
Alkaline phosphatase (U/L)	78	359	434	30-120
CSF analyzes				
Leukocytes (per mm^3)	187	-	0	<5
Neutrophiles (%)	55	-	0	0
Lymphocytes (%)	25	-	0	0
Monocytes (%)	21	-	0	0
Protein (g/L)	0.74	-	0.92	<0.45
Albumin (g/L)	0.4	-	-	<0.38
Glucose (mmol/L)	3.4	-	3.9	2.5-4.4
Microbiological analyses				
SARS-CoV2 Ag	NEG.	-	-	NEG.
HIV 1&2 Ab/Ag	NEG.	-	-	NEG.
Treponema pallidum Ig	NEG.	-	-	NEG.
TBEV IgM (U/ml)	10	-	-	< 10
TBEV IgG (U/ml)	< 30	-	-	< 100
TBEV IgM CSF-S Index	>2.49	-	-	< 1.5
TBEV IgG CSF-S Index	<1.5	-	-	< 1.5
TBEV NT50 CSF	-	-	640	≤10
TBEV NT50 S	-	-	1280	≤10
B. burgdorferi IgG S (AU/mL)	9	-	-	<10
B. burgdorferi IgM S (AU/mL)	6	-	-	<18
HSV1 DNA (CSF)	NEG.	-	-	NEG.
VZV DNA (CSF)	NEG.	-	-	NEG.
WNV RNA (CSF)	NEG.	-	-	NEG.
Autoimmune encephalitis panel CSF				
Aquaporin/MOG	NEG.	-	-	NEG.
NMDA – Receptor IgG	NEG.	-	-	NEG.
VGKC	NEG.	-	-	NEG.

CSF – Cerebrospinal fluid, HIV – Human Immunodeficiency virus, Ag – antigen, Ig – Immunoglobulin, S – serum, HSV1 – Herpes simplex virus 1, VZV – Varicella zoster virus, WNV – West Nile virus, MOG - myelin oligodendrocyte glycoprotein, NMDA - N-methyl-D-aspartate, VGKC - Voltage-Gated Potassium Channel.

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On the same day magnetic resonance imaging (MRI) was performed and global diffusion signal interference of the grey substance was detected, indicating encephalitis and long segment myelitis (Figure 1).

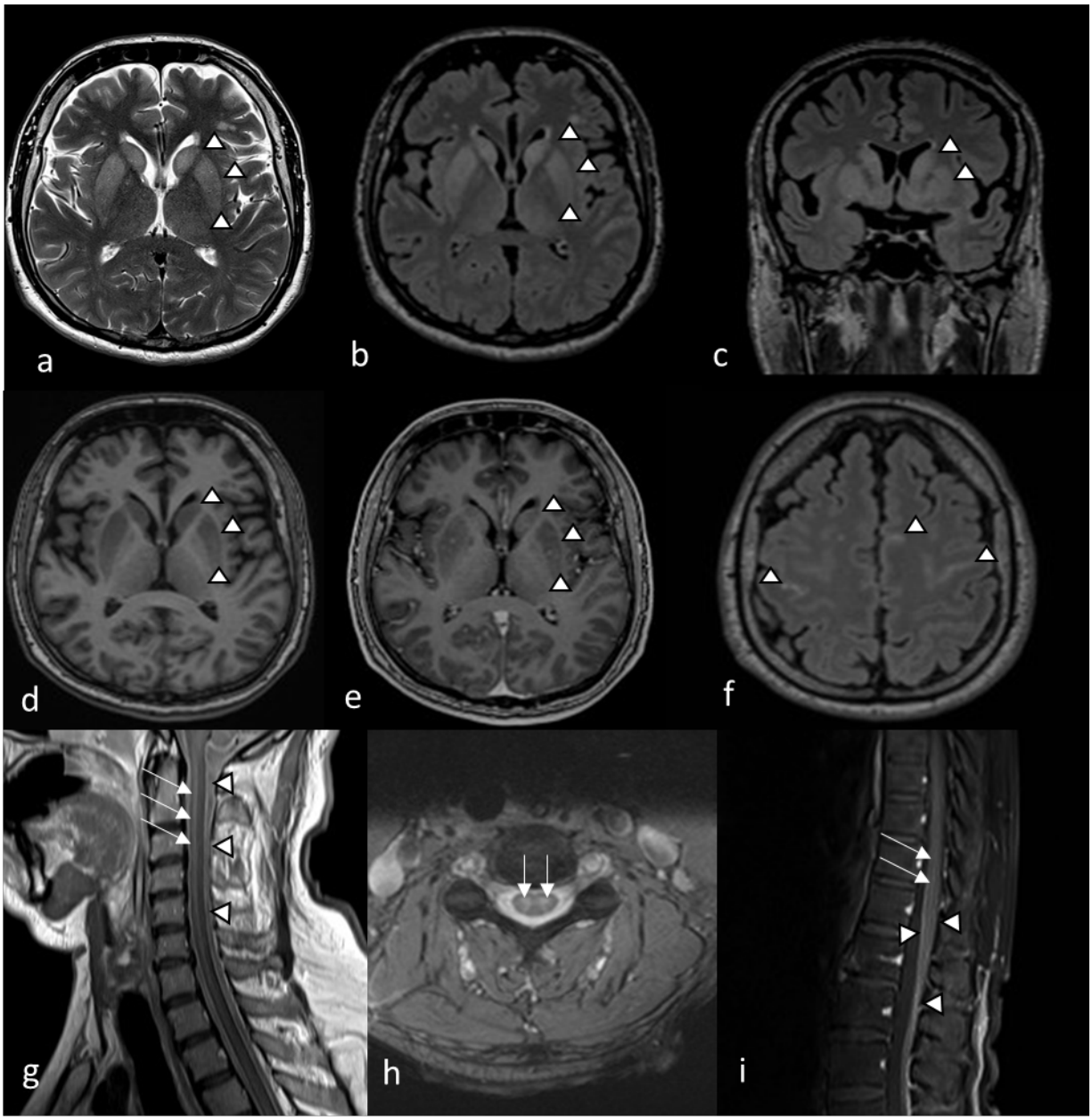

Figure 1. MRI findings on 14th day of illness in patient with TBE. MRI showed symmetric diffuse T2wi (a) and FLAIR (b) hyperintensity of basal ganglia, especially putamen and caudate nucleus, with slightly less pronounced increase in signal of both thalami (arrowheads) on axial (a,b) and coronal (c) images, consistent with edema. Bilaterally decreased T1wi signal in putamen and caudate nucleus (d) followed by patchy contrast enhancement (e) on axial images (arrowheads) implies basal ganglia inflammatory lesions. Meningeal contrast enhancement on FLAIR (f) and leptomeningeal contrast enhancement in cervical medulla (g) and medullary cone (i) correlates with meningeal/leptomeningeal inflammation (arrowheads). Symmetric T2wi signal increase found in cervical medulla (h) with contrast enhanced areas delineated in cervical (g), and lumbar spinal cord (i) correlates with myelitis (arrows).

Five days later (19th day of disease) patient was reallocated via helicopter from Switzerland to Clinical center Niš (Serbia) for future treatment. Combined antiedematous

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(mannitol solution), corticosteroid (dexamethasone), physical, anticoagulant and nutritive therapy was initiated. Eventually, patient gained consciousness and was able to understand and execute orders to open and close his eyes. Status related to quadriplegia, dysphagia and aphasia was unchanged. Subfebrility was persistent as during hospitalization in Switzerland. Electromyoneurography finding was normal (i.e., no signs of axonopathy, conduction block or demyelination). MRI didn't show any differences from status described on day 14. Complete list of laboratory examination conducted on day 19 is presented in Table 1.

On 27th day of disease, cytology and biochemical findings in CSF were unremarkable except detection of elevated protein levels (0.92 g/L). CSF and serum sample were forwarded to Pasteur Institute Novi Sad, for detection of TBEV neutralizing antibodies (TBEV-Nab). See the Supplement file 1 for details concerning Microneutralization assay. Both samples showed high neutralizing effect, suggesting acute TBEV infection. Complete list of laboratory examination conducted on day 27 is presented in Table 1.

In following period, the patient showed no neurological improvement, with same degree of quadriparesis and return to the state of disturbed consciousness. The further course of the disease was complicated by Ventilator Associated Pneumonia leading to fatal outcome on day 60.

3. Discussion

According to European Centre for Disease Prevention and Control (ECDC) report, majority of TBE cases in Europe are occurring from May to November. The incidence shows bimodal distribution with peaks in June-August and October [14]. The case described here is in accordance with current TBE incidence trends, since the first signs of disease and nervous system involvement occurred June. It should be highlighted that tick bite in our patient occurred during forest hiking, which is a high-risk activity for TBEV exposure in endemic territories, such as Switzerland [8]. For same reason, pre-exposure immunization against TBE is recommended for travelers visiting endemic countries [3,8,9]. Similar recommendation exists in Serbia, thus up to today neither of two vaccines available in Western Europe (i.e., Encepur and FSME-IMMUN) are not registered in Serbia for routine application [3].

In the majority of exposed persons, TBEV infection is asymptomatic. In approximately 30% of TBEV infection cases, person will develop fever and flu-like symphtoms after average incubation period of 7 days (range 2 - 28 days) and 20–30% of those will progress to complete clinical manifestation of TBE. According to anamnestic data related to tick-bite exposure, incubation period in our case (i.e., period between tick bite and fever onset) was 7 days and it is in accordance with previously published data [15].

If complete clinical manifestation of TBE occur, CNS involvement is most often presented as a pronounced meningeal syndrome, altered state of consciousness, cognitive dysfunction, ataxia, rigidity, convulsions, tremors, paralysis of cranial nerves and limb paresis [16,17]. Our patient developed complete clinical manifestation of TBEV infection, in the form of encephalomyelitis. In less than 10% of TBE cases, viral infection affects the anterior horn of the spinal cord which manifests as flaccid poliomyelitis-like paralysis or/and as paralysis of respiratory muscles, requiring artificial ventilation [18,19].

Concerning the virulence of different TBEV subtypes, TBEV-Sib and TBEV-Fe infection usually cause TBE with higher mortality rate compared to TBEV-Eu, where fatal cases occur in 0.5–2% of cases. Patient described here developed severe neurological form of the disease after tick bite within central European territory, suggesting possible (although not proven) exposure to subtype TBEV-Eu.

Possible reason for severe manifestation of TBEV infection in this case may be patients age, given that severe disease form and unfavorable outcome of TBE are associated with older age and male gender [16,20]. In addition, earlier study in tick infested patients from Serbia showed that men have higher risk of exposure to TBEV than women [13].

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The results of slightly elevated leukocyte count, neutrophilia and decreased lymphocytes found here are in accordance with previously reported [21]. The CRP levels were within reference values and did not reflect the patient status severity. The progression of aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, and alkaline phosphatase values throughout the second phase can be explained with maintenance of viremia, suggesting an effect of the virus on the bone marrow and liver [22]. Elevated CK levels could be consequence of muscle tissue affection presented as myositis, which is shown by some authors as a prognostic sign for a severe clinical course [23]. The results of CSF analysis in our case are in accordance with other TBE cases, since elevated level of neutrophils, lymphocytes, and proteins were detected [21].

In addition to laboratory diagnostic, several imaging methods can be used to assess disease severity and the degree of neurological involvement. The virus shows a specific predilection to the basal ganglia and the thalamus [17] It is considered for CT to have lower sensitivity in the diagnosis of TBE compared to MRI, probably due to improper delineation of involved areas, leading to underestimation of the extent of encephalitis. Typical TBE changes include hypodense regions mainly in the basal ganglia and the thalamus [17]. On the other hand, MRI abnormalities can be found in 20-44% acute TBE cases [16–18].

The MRI finding of our patient is very significant due to the simultaneous involvement of meninges, basal ganglia (putamen and caudate nucleus), thalamus (bilaterally), meninges, cervical and lumbar spinal cord without significant improvement in the control scan. The extent and the dynamics of the process explains the progressive and severe clinical presentation and the poor outcome of the disease. The increased extension of cerebral MRI lesions in TBE patients is associated with a more severe clinical course [24].

Given that there are no available anti-TBE vaccines in Serbia, the case described here is highlighting the necessity for introduction of immunization against TBEV in persons travelling from Serbia to TBE-endemic territories (e.g., Croatia, Slovenia, Hungary, Slovenia, Slovakia, Czech Republic, Switzerland, etc.). Since previously published data suggest exposure of Serbian population to TBEV [11–13], implementation of immunization

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Supplementary file 1 – Microneutralization assay procedure

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