

Tick-borne Encephalitis in Professionally Exposed Persons after Complete Primary Vaccination

Krpeljni encefalitis kod profesionalno izložene osobe nakon uredno provedenog primarnog cijepljenja

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Case report/Prikaz bolesnika

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Abstract

In this paper we present a case report of tick-borne encephalitis (TBE) in a professionally exposed person (forestry worker) who acquired this infection three years after he had received a complete primary vaccination. The patient reported multiple tick bites, the last one eighteen days prior to disease onset. The TBE diagnosis was confirmed according to the European Center for Disease Prevention and Control case definition of TBE by clinical criteria (meningitis), epidemiological link (exposure to tick bites in an endemic area) and laboratory criteria (detection of TBEV specific IgM and IgG antibodies in CSF and serum samples). The case presented indicates the need of awareness of possible TBE even in persons who have received complete vaccination, especially in the professionally exposed ones or those exposed to multiple tick bites.

Sažetak

U radu prikazujemo slučaj krpelnog encefalitisa (KE) kod profesionalno izložene osobe (šumar) koja je oboljela tri godine nakon uredno provedenog primarnog cijepljenja. Pacijent je naveo višestruke ugrize krpelja, od kojih je posljednji bio osamnaest dana prije početka bolesti. Dijagnoza KE potvrđena je prema kriterijima Europskog centra za kontrolu bolesti (ECDC) na temelju kliničkih (meningitis), epidemioloških (izloženost krpeljima u endemskom području) te laboratorijskih kriterija (dokaz specifičnih IgM i IgG protutijela za KE u uzorcima seruma i cerebrospinalnog likvora). Prikazani slučaj naglašava potrebu za promišljanjem o mogućoj pojavi KE i kod osoba kod kojih je provedeno kompletno cijepljenje, osobito profesionalno izloženih osoba te onih izloženih čestim ugrizima krpelja.

Introduction

Tick-borne encephalitis (TBE) is an emerging zoonosis caused by the tick-borne encephalitis virus (TBEV). The TBE is one of the most important diseases of the central nervous system in many European countries with an increasing incidence over the past few decades. In Europe and Asia, between 10,000 and 15,000 TBE cases are reported annually. Most cases of TBE occur during the highest period of ticks activity in Central Europe, mainly from April to November [1]. In addition to tick bite, the disease can also be transmitted through consumption of unpasteurized milk or dairy products from infected livestock [2]. There is a broad range of severity grade of TBEV infection, ranging from an asymptomatic infection to a severe meningoencephalomyelitis. In European countries, TBE presents as meningitis in about 50% of patients, as meningoencephalitis in 40%, and as meningoencephalomyelitis in 10% [3]. Although the disease can be efficiently prevented by active immunization, vaccination failures have been described, especially in elderly people [4-6].

In Croatia, TBE is endemic in north western regions, but infections are reported in all continental counties with an average of 36 (range 11-87) cases registered on annual basis [7]. Vaccination against TBEV is not mandatory in Croatia, but is recommended to persons exposed to TBE risk, such as forestry workers and hunters or those frequently visiting the forests and grasslands where ticks populations are high. We present the case of TBE in a young professionally exposed person who has received a complete primary vaccination.

Case report

In May 2017, a 36-year-old man, forestry worker, was hospitalized at the Clinic for Infectious Diseases on the sixth day of the illnesses. The disease was manifested by daily fever up to 40°C, headache, nausea, diarrhoea and vomiting. The patient reported multiple tick bites, the last one 18 days prior to disease onset (Gorski Kotar). In 2013/2014, he received a complete primary vaccination with three doses of TBEV vaccine (the last one in

April 2014). At the moment of the admission, the patient was febrile (38°C), oriented, and mildly dehydrated. The physical and neurological examination indicated no problems, except the neck stiffness. The patient was initially treated with acyclovir (until the completion of virology results) with a supportive (antiedematous) therapy. From the fourth day of hospitalization, the patient was afebrile and without a headache. The patient was monitored during the four months and he has fully recovered.

Laboratory and Neuroimaging Results

Routine laboratory tests (Table 1) indicated an elevated white blood cell (WBC) count ($14.1 \times 10^9/L$). The patient's C-reactive protein level amounted to 14.4 mg/L, and his erythrocyte sedimentation rate to 23 mm/h. Other laboratory parameters were within normal range. Cerebrospinal fluid (CSF) analysis revealed a WBC count of $132 \times 10^6/L$ (76% lymphocytes), protein level of 0.753 g/L and glucose level of 3.61 mmol/L. Electroencephalogram (EEG) indicated slow diffuse dysrhythmia and computed tomography of the brain was normal. Normalization of EEG finding occurred after four months from initial evaluation.

Virology Results

CSF, serum and urine samples were collected and tested for the presence of TBEV antibodies and/or TBEV RNA. TBEV IgM/IgG antibodies and IgG avidity were detected using enzyme-linked immunosorbent assays (ELISA; Euroimmun, Lübeck, Germany). To exclude cross-reactivity with other flaviviruses, serum and CSF samples were also tested for West Nile virus (WNV) and Usutu virus (USUV) antibodies. TBEV RNA was detected using a real-time RT-PCR according to the protocol of Schwaiger et al. [8], WNV RNA according to the protocol of Tang et al. [9] and USUV RNA according to the protocol of Nikolay et al. [10].

Virology results are presented in the Table 2. Although cross-reactive antibodies with WNV and USUV were detected in serology tests, very high values of TBEV IgM and IgG antibodies in both serum (IgM ratio 5.01; IgG

Table 1. Laboratory findings in patient with tick-borne encephalitis

Tablica 1. Laboratorijski nalazi u bolesnika s krpeljnim meningoencefalitisom

Parameter	Value	Reference values
BLOOD		
White blood cells; WBC ($\times 10^9/L$)	14.1	3.4 - 9.7
Red blood cells; RBC ($\times 10^{12}/L$)	4.80	3.86 - 5.08
Hemoglobin (g/L)	149	119 - 157
C-reactive protein (mg/L)	14.4	< 5
Erythrocyte sedimentation rate	23	< 12
Aspartate-aminotransferase; AST (U/L)	15	8 - 30
Alanine-aminotransferase; ALT (U/L)	26	10 - 36
Gamma-glutamyltransferase; GGT (U/L)	91	9 - 35

Urea (mmol/L)	4.6	2.8 - 8.3
Creatinine (μ mol/L)	99	49 - 90
Glucose (mmol/L)	5.8	4.4 - 6.4
CEREBROSPINAL FLUID		
WBC ($\times 10^6/L$)	132	< 5
Lymphocytes (%)	76	-
Proteins (g/L)	0.753	0.170 - 0.370
Glucose (mmol/L)	3.61	2.5 - 3.3

Table 2. Virology results in patient with tick-borne encephalitis**Tablica 2.** Rezultati virusološke dijagnostike u bolesnika s krpeljnim meningoencefalitismom

Sample	Day tested	TBEV IgM (ratio)*	TBEV IgG (RU/ml)**	WNV IgM (ratio)*	WNV IgG (RU/ml)**	USUV IgG (RU/ml)**	TBEV/WNV/USUV RT-PCR
Serum I	15	5.01	>200	1.29	155	98	-
Serum II	29	4.20	>200	2.56	156	120	-
Serum III	43	2.82	>200	1.21	178	198	-
CSF	20	4.35	191	0.10	24	16	Neg
Urine	15	-	-	-	-	-	Neg

*ratio <0.8 negative; 0.8-1.1 borderline; >1.1 positive

**RU/ml <16 negative; 16-22 borderline; >22 positive

>200 RU/ml) and CSF (IgM ratio 4.35; IgG 191 RU/ml) at the initial testing indicate a TBEV infection. In addition, TBE was further supported by antibody dynamics, i.e. a decline of IgM antibodies in the two consecutive serum samples (ratio 4.20 and 2.82, respectively) with continuously very high IgG levels (>200 RU/ml). Since the patient was vaccinated against TBEV, IgG avidity was high (98%). TBEV, WNV and USUV RNA was not detected in CSF and urine samples. CSF sample was additionally tested for the presence of other neuroinvasive viruses: herpes simplex viruses 1/2, enteroviruses, Toscana virus, Tahyna virus and lymphocytic choriomeningitis virus using PCR or RT-PCR. All the results were negative. PCR and serology for *Borrelia burgdorferi* were also negative.

Discussion

Although TBEV vaccine failure is rare, in particular after completed vaccination, there are several reports of TBEV infection in incompletely and completely vaccinated persons. A recently published study from Slovenia, an endemic country for TBE, reported that 1.7% of vaccinated persons have developed TBE, 64.1% of whom had received complete basic vaccination and the others had received only two doses prior to disease onset. In addition, the acute illness in patients with TBE breakthrough was shown to be more severe than in unvaccinated persons [11]. Moreover, there are few reports of a fatal outcome of TBE in vaccinated persons [12].

The patient presented in this report received the last dose of TBEV vaccine in April 2014, but did not receive

a booster dose thereafter. He was continuously exposed to multiple tick bites (professional exposure) and developed symptoms of TBE at the beginning of May 2017, 36 months upon the last vaccination. Similar results were observed in a Slovenian study, i.e. the median time interval between the last dose of TBE vaccine and illness onset was 36 (1-180) months [11].

Due to different and sometimes confusing antibody kinetics in vaccinated patients with TBEV infection, these infections may be overlooked [13]. It is well known that TBE patients have detectable serum IgM antibodies and the vast majority of them also has IgG antibodies at the beginning of the neurologic phase of the disease [11, 14]. In contrast, patients who develop TBE breakthrough, generally have very high TBEV IgG antibody levels, while IgM antibody response may be absent or low in the first days of the meningoencephalitic phase [11, 15]. In addition, TBEV IgG antibodies are of high avidity in vaccinated persons [11]. According to the European Center for Disease Prevention and Control case definition of TBE, the diagnosis of TBE in our patient was established by clinical criteria (symptoms of meningitis), epidemiological link (exposure to tick bite in an endemic area) and laboratory criteria for a confirmed case (detection of TBEV specific IgM and IgG antibodies in both CSF and serum) [16]. Since the patient was vaccinated against TBE, IgG antibodies were at very high level and showed high avidity. TBEV RNA was not detected in CSF and urine samples.

The case presented in this report indicates the need of awareness of possible TBE, even in completely vac-

inated persons, especially in those exposed to multiple tick bites [7]. Therefore, TBE should remain an important differential diagnosis in these patients. In addition, clinicians should keep in mind that the presence of TBEV IgG antibodies in the absence of IgM antibodies at the onset of clinical symptoms does not exclude TBE in previously vaccinated patients [12].

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