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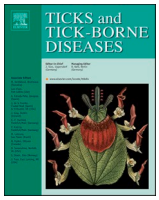

Short communication

A fatal case of tick-borne encephalitis in an immunocompromised patient: case report from Northeastern Poland and review of literature

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ABSTRACT

Tick-borne encephalitis (TBE) is an infectious illness of the central nervous system caused by the TBE virus, which is commonly transmitted through a tick-bite. TBE is endemic in Europe and mid-Asia. In this study, we report a case of a 36-year-old woman, living in Northeastern Poland, with a history of double corneal transplantation and post-transplant immunosuppressive therapy who was admitted to hospital because of progressive weakness, acute headache, nausea, vertigo, vomiting, and fever. The patient was diagnosed with TBE. However, the diagnosis was challenging as the initial serological tests for antibodies against the TBE virus were negative. We want to raise the awareness among the clinicians that the course of TBE is often unpredictable and that it tends to be more severe in immunocompromised individuals.. Delayed production of antibodies against TBE virus, which might inhibit the diagnosis of the disease, is observed in some immunocompromised patients.

1. Introduction

Tick-borne encephalitis (TBE) is a central nervous system disease caused by an RNA virus belonging to the *Flaviviridae* family. TBE is endemic in central and Eastern Europe, Siberia, the Russian Far East, Northern China, and Japan (Bogovic, 2015; Stefanoff et al., 2013). The TBE virus (TBEV) is mainly transmitted by *Ixodes* spp. tick bites and rarely through the consumption of dairy products or unpasteurized milk from infected livestock (Bogovic, 2015).

In Poland, TBE is endemic and approximately 200–300 cases are reported each year. The region with the highest TBE occurrence is Northeastern Poland, particularly Podlaskie Voivodeship, from which nearly 50 % of all TBE cases in the country have been reported. Over the past decade, the annual incidence of TBE in Podlaskie Voivodeship varied from 6.5 to 13.5/100,000 inhabitants while the overall incidence of TBE in Poland ranged from 0.39 to 0.92/100,000 inhabitants (Sadkowska-Todys et al., 2020). However, the incidence of TBE can be underestimated since the diagnostic tests for this condition are not performed routinely in places in which the disease rarely occurs (Stefanoff et al., 2018). The incubation period of TBE generally lasts between 7 and 10 days. The disease is characterized by a biphasic course. In the first phase, the predominating symptoms include low-grade fever, fatigue, malaise, headache, and arthralgia. Neurological manifestations are the hallmark of the second phase with a clinical spectrum ranging from mild meningitis to severe encephalitis, which may be accompanied by myelitis and acute flaccid paralysis (Kaiser, 2012; Lindquist and Vapalahti, 2008). In patients that reach the neurological phase, TBE presents as meningitis in about 50 % of cases, meningoencephalitis in 40 %, and meningoencephalomyelitis in 10 % of patients (Kaiser, 2012). Age, the severity of illness in the acute stage, and low initial neutralizing antibody titres are associated with illness severity (Bogovič et al., 2018; Kaiser and Holzmann, 2000; Lindquist and Vapalahti, 2008). TBE can be fatal, especially in immunosuppressed patients (Zajkowska et al., 2011).

2. Case report

A 36-year-old female with a history of double corneal transplantation and post-transplant immunosuppressive therapy was admitted to the regional hospital because of progressing weakness, acute

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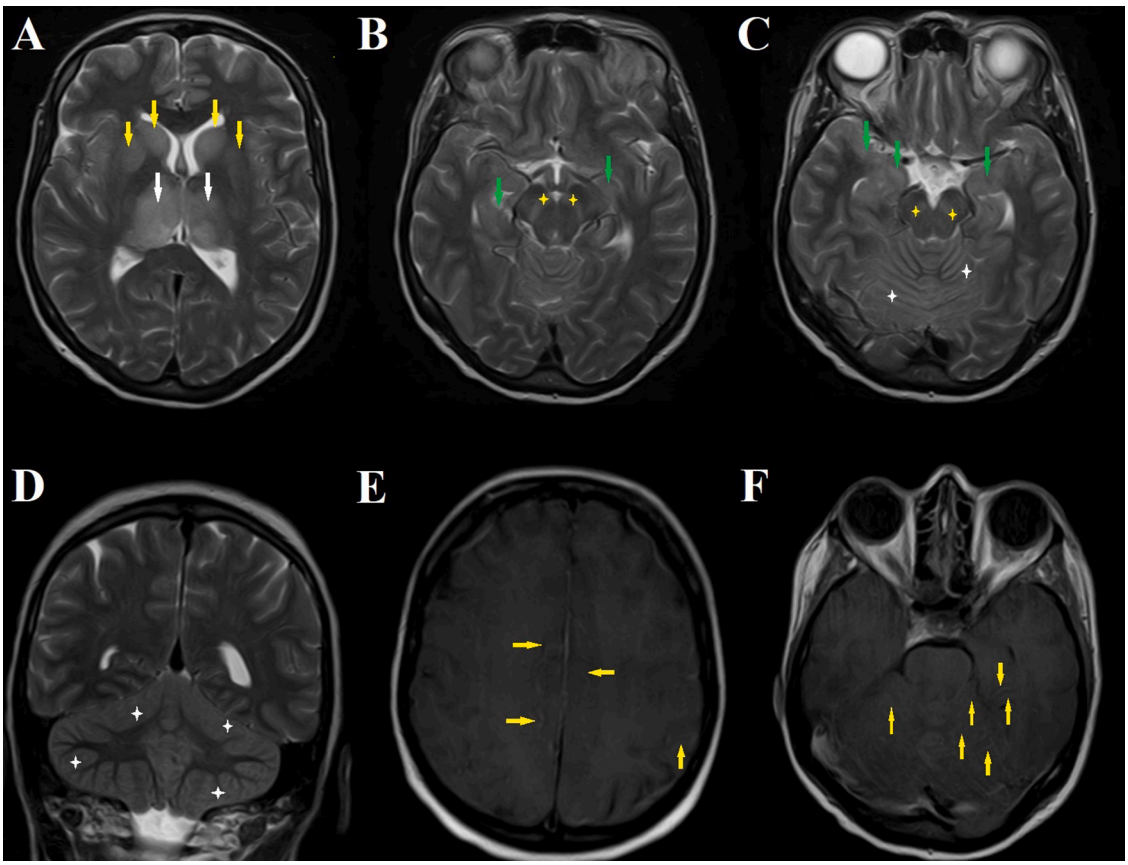

Fig. 1. Initial magnetic resonance image (MRI) of the brain of a 36-year-old woman diagnosed with tick-borne encephalitis (TBE). Axial T2-weighted (A, B, C), and coronal T2-weighted (D) depict bilateral hyperintensity in the thalami (white arrows), caudate, and lentiform nuclei (yellow arrows with a predominance on the right side), a bilateral hyperintense signal at the medial temporal lobes (green arrows) and midbrain (yellow asterix), and hyperintense signal and mild swelling of the cerebellar cortex (white asterix). Axial contrast-enhanced T1-weighted images (E, F) demonstrate mild leptomeningeal contrast enhancement that affected the front-parietal-temporal regions and extended down into the cerebellum (yellow arrows). No visible parenchymal enhancement within the thalami and basal ganglia (not shown) was visible.

headache, nausea, dizziness, vomiting, and fever for over a week. The patient lived in an area of Poland with a medium prevalence of TBE and had not been vaccinated against TBE. According to the family, she did not have any tick bites. Past medical history included a corneal transplant due to bullous keratopathy and endothelial insufficiency in the left eye. She was receiving immunosuppressive therapy (methylprednisolone 20 mg/day, mycophenolate mofetil 2 × 750 mg/day) and was receiving acyclovir (4 × 400 mg/day) as antiviral prophylaxis for the past six months. Four weeks prior to hospital admission, she had an upper respiratory tract infection with flu-like symptoms for which she received antibiotic therapy (amoxicillin 1 g/24 h). During the first two days of hospitalization, progressive drowsiness appeared. The patient had severe dizziness, nystagmus, and disturbances of consciousness. No meningeal signs or additional neurological deficits were found. Due to her deteriorating clinical condition, she was transferred to the Department of Infectious Diseases and Neuroinfections with suspicion of encephalitis. The neurological examination upon admission revealed impaired consciousness, mutism, weakness of left upper and lower extremities, positive Babinski's sign on both sides, roving eye movement, and periodic nystagmus with right-sided quick phase. Blood samples were collected for cultures to rule out potential causes of sepsis and were negative for *Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae, Listeria monocytogenes*, and *Streptococcus agalactiae*. The patient received antiedema treatment (dexamethasone 4 × 4 mg/day), antiviral treatment (acyclovir intravenous 3 × 750 mg/day) and empiric antibiotic therapy (ceftriaxone 2 g/day).

Cerebrospinal fluid (CSF) analysis revealed pleocytosis of 104 cells/μl (lymphocytes 84 %, monocytes 9 %, macrophages 1 %, neutrophils 0 %, plasmocytes 6 %), a protein level of 120 mg/dL, and a glucose level of 49 mg/dL. Polymerase chain reaction (PCR) of CSF was negative for Herpes simplex viruses 1 and 2, Epstein–Barr virus, cytomegalovirus, and human Herpes virus 6 (HSV-1, HSV-2, EBV, CMV, and HHV-6, respectively). CSF was negative for antibodies against TBE virus.

During the first 48 h of hospitalization, three tonic–clonic seizures occurred. The patient had decreased saturation and periodic temperature increases followed by tachypnea, tachycardia, features of pulmonary edema, and dysphagia. The patient was immediately transferred to the intensive care unit (ICU). In the ICU, the patient was unconscious, with no logical contact and minimal reaction to pain stimuli. Due to respiratory failure, she was intubated and ventilated mechanically. Physical examination revealed features of left lung atelectasis. The patient underwent bronchoscopy, during which bronchial obstruction by inflammatory exudate was visualized and the blockage was removed. The patient had tachycardia (approximately 115 beats per minute), hypotension (approximately 85/50 mmHg), no fever (36.9 °C), and recurrent seizures. A pharmacological coma was induced. The initial magnetic resonance image (MRI) as shown in Fig. 1 revealed massive changes in both sides of the thalamus, midbrain, cerebellum, basal ganglia, and medial temporal lobes that could have corresponded to Creutzfeldt–Jacob's disease. CSF analysis for protein 14–3–3 was performed, and the results were negative.

Shortly after ICU admission, frequent jerky movements of lips appeared. The patient was treated with antiepileptic drugs in increasing doses throughout the whole hospitalization period when the symptom

Table 1
TBE serology of the patient in the presented case.

	At admission	3 weeks later	Another 3 weeks later
CSF anti-TBE IgM	Negative	Positive (100.9 U/ml)	Positive (110.9 U/ml)
CSF anti-TBE IgG	Negative	Positive (991.1 U/ml)	Positive (2681.7 U/ml)

returned. Electroencephalography (EEG) was performed and revealed abnormal periodic/pseudoperiodic paroxysms of triphasic or sharp waves of 0.5 to 2.0 Hz against a slow background.

Although first sample of CSF was negative for antibodies against TBE virus, the second (IgM 100.9 U/ml IgG 991.1 U/ml, Virion Serion) and third samples (IgM 110.9 U/ml IgG 2681.7 U/ml, Virion Serion) were positive (Table 1). Independent evaluation of serum and CSF samples was performed in the Medical University of Vienna, Department of Virology and confirmed TBE infection: (1) serum ELA FSME® Virus IgM positive, IgG (VIE units) 8760, NT FSME Virus NT 960; and (2) CSF FSME Virus IgM positive, IgG (VIE units) 974, NT FSME Virus NT 960.

During the next four months of hospitalization in the ICU, no clinical improvement occurred. Repeated MRI showed the involvement of further structures and secondary lesions (Fig. 2). The patient was maintained in a pharmacological coma with no spontaneous breathing function. Dynamic fluctuations in blood pressure (hypotension–hypertension) and transient hyperthermia were observed. Neurological deficits in the form of total lack of response to stimuli, anisocoria and flaccid tetraparesis gradually increased. Due to lack of therapeutic possibilities, i.v. immunoglobulins were administered without any effect. The outcome of the disease, despite the symptomatic treatment, was fatal.

3. Discussion

TBE is a disease that may present as meningitis, meningoencephalitis, or meningoencephalomyelitis. The European TBEV subtype typically produces a biphasic course and tends to be less severe although it may be fatal in 1- 2 % of cases (Pettersson et al., 2014). Many risk factors, including patient age, immunosuppression, and comorbid diseases, influence the severity of TBE (Zajkowska et al., 2011). A number of factors contribute to the suppression of the immune system: (1) human immunodeficiency virus (HIV) infection, (2) treatment for autoimmune conditions, (3) solid organ transplantation, (4) malignancies, and/or (5) cancer chemotherapy (Harpaz et al., 2016). In the presented case a major factor compromising the patient's immune system was post-transplant immunosuppressive therapy. Many new immunosuppressive agents have been introduced over the past several years (Meneghini et al., 2021). The number of immunosuppressed patients may be increasing because of the greater life expectancy among immunocompromised adults due to improvements in medical care in addition to new indications for immunosuppressive treatments (Harpaz et al., 2016). Several fatal cases of TBE have been described in immunocompromised patients (Table 2 in supplementary file). Factors, that decreased patients immunity, were among other medications for autoimmunological disorders (Knight et al., al.,2017; Steininger et al., 2017; Sendi et al., 2017; De Bruijn et al., 2015; Zajkowska et al., 2011). TBEV can be a potential threat to organ transplant recipients. Not only does the immunosuppression make them more prone to developing a severe form of the disease, but TBEV is also transmittable through organ

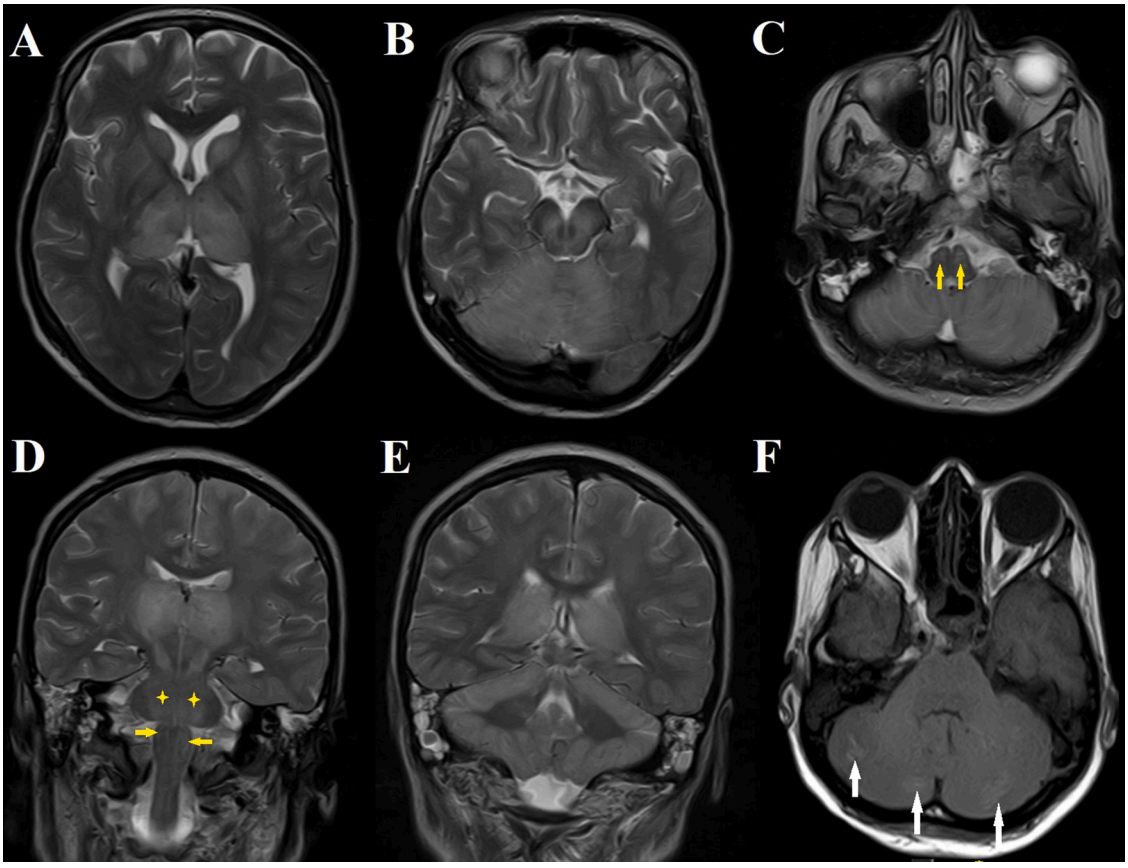

Fig. 2. Final follow-up MRI. Axial (A, B, C), and coronal (D, E) T2-weighted images show increased involvement of the basal ganglia, thalami, midbrain and cerebellum, and additional involvement of the pons (yellow asterix) and medulla oblongata (yellow arrows). Axial non-contrast-enhanced T1-weighted image (F) demonstrates secondary cortical hyperintensities along bilateral cerebellar folia consistent with cortical laminar necrosis (white arrows). At the time of imaging, the patient was intubated, which resulted in opacified sinuses and mastoid air cells.

Table 2
Demographic information, clinical features and MRI findings of patients with fatal European TBE.

Age (yrs)/ sex	Vaccination status	Tick bite history	Risk factors	Symptoms	Confirmation of the disease	MRI	References
36/F	unvaccinated	No history of tick bite	Immnosupresssive therapy due to corneal transplant (methylprednisolone, mycophenolate mofetil)	Initial: flu-like symptoms Later: headache, vomiting, nausea, dizziness, fever, nystagmus, disorientation, mutism, dysphagia, bilaterally positive Babinski sign, respiratory insufficiency, tetraparesis	Initially anti-TBEV IgM and IgG were negative in serum and CSF. Later on, IgM and IgG were positive in both serum and CSF.	bilateral hyperintensities in the thalami, caudate nuclei and putamen were observed in T2-weighted images. In the fourth MRI, in T1-weighted image hyperintensities within the cortex of both cerebral hemispheres and foci of pathological contrast enhancement in the thalamus and cerebellum were seen.	This article
66/M	unvaccinated	Frequently bitten by ticks	Chronic lymphatic leukemia	Initial: persistent fever, later on the patient developed tetraparesis and urinary retention	CSF analysis showed pleocytosis. Initial sample of serum and CSF were negative for TBEV IgM and RNA. One week after hospitalization, CSF was positive for TBEV IgM but his CSF, serum, and urine were RNA negative.	increased signal in cerebellar vermis, facial nerves, cortical sulci, and radicular regions	Kuivanen et al. 2018
54/M	–	No history of travel to TBE endemic areas	Liver transplantation (corticosteroids, tacrolimus) from a TBEV-infected donor	initial :fever, headache he remained febrile, developed dysarthia, dysphagia, and eventually tetraplegia, and his mental status progressed to coma. he died 69 days after admission due to septic shock and multiorgan failure	postmortem detection of tbev by rt-pcr and ngs in brain tissue	Not described	Lipowski et al., 2017
27/M	–	No history of travel to TBE endemic areas, no tick bite history	Kidney transplant recipient from a TBEV-infected donor tacrolimus, corticosteroids, and mycophenolate mofetil	initial: fever, headache, vertigo, and vomiting at admission, the patient presented with meningeal signs: nystagmus, dysarthia and aphasia, paralysis of cranial nerves iii and iv, and bilaterally positive babinski sign, the patient progressed to coma within 2 days and eventually required mechanical ventilation. he died 36 days after admission	postmortem detection of tbev by rt-pcr and ngs in brain tissue	Not described	Lipowski et al., 2017
48/M	–		Kidney transplant recipient from a TBEV-infected donor tacrolimus, corticosteroids, and mycophenolate mofetil	2 days of fever up to 39.5 °c, complaints of headache, double vision, and weakness in lower extremities. at admission the patient presented with nystagmus and meningeal signs, and his consciousness was impaired his mental status progressed to coma, and he eventually required assisted ventilation. the patient died 83 days after admission.	postmortem detection of tbev by rt-pcr and ngs in csf	Not described	Lipowski et al., 2017
48/F	unknown	unknown	Immunotherapy for systemic lupus erythematosus	cough, fever and malaise, headache, gait instability and pain radiating from neck to left upper limb,	Initially serology was negative. Later on, serologic tests showed positive IgM and IgG for TBEV with increasing titer in the following days	MRI was repeated with MR-angiography (MRA), showing hyperintense lesions in thalamus and caudate nucleus on FLAIR images	de Bruijn et al. 2015

(*continued on next page*)

Table 2 (*continued*)

Age (yrs)/ sex	Vaccination status	Tick bite history	Risk factors	Symptoms	Confirmation of the disease	MRI	References
				downbeat nystagmus and paresis of the left upper limb, tetraplegia and respiratory insufficiency			
12/M	unvaccinated	positive	haemophagocytic lymphohistiocytosis	pyrexia, mild neck stiffness, then: severe neck stiffness, tremor, and general weakness, rapidly progressing to quadriplegia, respiratory insufficiency, and coma	Initial lumbar puncture showed normal result. TBE IgG and IgM (ELISA) were negative Repeated CSF study revealed raised protein and lymphocytes. TBE serology at this time was highly positive in both IgG and IgM (EIA TBE Virus IgM, EIA TBE Virus IgG; Test-Line Clinical Diagnostics, Czech Republic)	Not described	Chmelik et al. 2016
67/M	Vaccinated with 3 doses	unknown	Farmer, treatment with methotrexate and prednisone for rheumatoid arthritis	headaches, fever, nausea, and vomiting, disorientation, somnolence, neck stiffness, increased tonicity of the upper and lower extremities, increased jerks of the lower limbs, and myoclonic movement	high anti-TBEV antibody titers in serum TBEV IgG and IgM levels RT-PCR for the detection of TBEV was performed on postmortem samples from the cerebellum and spinal cord. High copy numbers of viral RNA were found in both samples. Immunohistochemical analysis for the demonstration of TBEV antigen was performed on tissue samples of the spinal cord and the cortical cerebellum.	Initial MRI: no abnormalities Cranial MRI scan on day 16 showed slight hyperintensity in the region of the left lateral thalamus	Sendi et al., 2017
28/F	Unvaccinated	positive	rituximab treatment (systemic lupus erythematosus)	Initial symptoms: high fever and headache. Rapid deterioration with dizziness, nystagmus, cervical rigidity and disorientation	CSF analysis showed moderate pleocytosis with mononuclear dominance. Serum antibody titres against TBEV showed increasing IgM and eventually IgG levels.	MRI of the brain showed marked symmetrical signal changes in both thalami	Knight et al., 2017
69/M	Vaccinated		rituximab treatment (rheumatoid arthritis)	Initial symptoms: fever, malaise and vomiting. Rapid deterioration within 24 h with disorientation, somnolence and cervical rigidity. Passed away 3 weeks after initial symptoms.	CSF analysis showed pleocytosis, but initial serology for TBEV was negative. Repeated A postmortem analysis of brain tissue demonstrated TBEV RNA. Analysis of serum and CSF showed IgG antibodies against TBEV in low titres in serum (vaccination), but no IgM antibodies and no intrathecal antibody production.	MRI scans demonstrated progressive signal changes in both thalami and additional lesions in the mesencephalon and cerebellum.	Knight et al., 2017
71/M	unvaccinated	positive	Methotrexate, cytarabine treatment (relapsing blastic plasmacytoid dendritic cell)	Initial symptoms: fever, weakness paresthesia; then paresis of left upper limb and opsoclonus; worsening of neurological status: disorientation, aphasia, involuntary movements, severe muscle hypotrophya, uncollaborative.	CSF analysis showed abnormalities: 80 cells/mmc, >90 % lymphocytes, slightly increased protein; detection of IgG and IgM in serum; positive quantitative RT PCR in blood and urine	Not performed	Caracciolo et al., 2015

transplantation in the case of TBE-infected donors (Lipowski et al., 2017). Severe TBE infection has also been reported in patients treated for proliferative diseases (Chmelík et al., 2016; Kuivanen et al., 2018; Caracciolo et al., 2015).

In TBE caused by the European subtype, 72 %–87 % of meningoencephalitis cases have a biphasic disease course. Monophasic and short biphasic courses were reported to be associated with more severe disease (de Bruijn et al., 2015; Lindquist and Vapalahti, 2008). Our patient had a biphasic course of TBE with initial flu-like symptoms followed by the development of an acute neurological phase. However, possibly due to the immunosuppression, the severity of the disease was overwhelming. A tick bite is unnoticed in about one-third of patients, and

initial symptoms are not specific, which makes the diagnosis of TBEat that early time challenging (Lindquist and Vapalahti, 2008) . CSF examination typically shows pleocytosis with a dominance of mononuclear cells. However, at first, polymorphonuclear cells may predominate (Grygorczuk et al., 2018). The diagnosis of TBE can be made by the detection of antibodies to TBE in CSF, their fourfold increase in serum, isolation of the virus, or detection of viral antigens and/or genomic sequences in blood, CSF, and/or tissue (Holzmann, 2003) . IgM and IgG antibody responses are usually detectable in CSF several days later than in serum (Lindquist and Vapalahti, 2008). Delayed production of antibodies to TBE virus, which may complicate diagnosis, can be observed in immunocompromised patients (Chmelík et al., 2016; de Bruijn et al., 2015; Knight et al., 2017; Kuivanen et al., 2018). Table 2 represents a list of cases of immunocompromised patients reported in the literature.

MRI abnormalities are reported in approximately 18 % of patients with TBE. Lesions are located mainly in the thalamus, cerebellum, brainstem, and caudate nucleus. EEG is abnormal in 77 % of the patients. However, the findings from MRI and EEG are nonspecific (Lindquist and Vapalahti, 2008). Although MRI abnormalities in TBE infection resemble those of other diseases (e.g. Creutzfeldt-Jakob disease, Leigh disease, Wilson disease, and infections with other viruses of the family *Flaviviridae*), the predilection for thalami, basal ganglia, cerebellum, and the anterior horns of the spinal cord can suggest TBE in certain clinical circumstances (Horger et al., 2012; Zawadzki et al., 2017). In our patient, bilateral hyperintensities in the thalami, caudate nuclei, and putamen were observed on the T2-weighted images. In the fourth MRI, on the T1-weighted image, hyperintensities within the cortex of both cerebral hemispheres and foci of pathological contrast enhancement in the thalamus and cerebellum were seen.

Treatment of TBE is mainly based on symptoms. The disease can be effectively prevented by vaccination. However, a standard TBEV vaccine schedule may not provide enough cellular immunogenicity in immunosuppressed patients, and TBE can occur even with a full course of vaccination (Sendi et al., 2017). In a study conducted by Hertzell et al. (2016), post-vaccine levels of neutralizing antibodies against TBE virus were evaluated in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors and/or methotrexate when compared with healthy matched controls. It was stated that the standard TBE vaccination schedule does not provide protective immunogenicity in the group of immunosuppressed patients and these patients are at higher risk of vaccination failure.

In the presented case, we made an attempt of treatment with immunoglobulins. Unfortunately, we were not able to investigate the preparation for specific antibodies against TBE virus. The results of some studies indicate that intravenous immunoglobulin with a proven high antibodies against TBE virus titre might be one of the therapeutic options for individuals with severe TBE (Elsterova et al., 2017). What is more, there is a great geographic variability in immunoglobulins antibody content, including level of antibodies against TBE virus (Rabel et al., 2012).

A limitation of our study is that we did not include molecular studies (detection of the virus RNA in the serum or CSF). Furthermore administered immunoglobulins did not contain specific antibodies against TBE virus.

4. Conclusions

The clinical course of TBE is unpredictable and in immunocompromised patients, tends to be more severe. Delayed production of antibodies against TBE virus is observed in some of the immunocompromised patients and may impede the diagnosis of the disease. Patients undergoing immunosuppressive therapy should be warned of this risk and advised to avoid tick bites, especially in TBE-endemic areas.

Author statement

All authors have contributed to the work and agree with presented findings. The manuscript has neither been published nor submitted to publication elsewhere. The study was approved by the Bioethics Committee at Medical University of Białystok, Poland. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Agata Czarnowska: Conceptualization, Investigation, Writing – original draft. **Monika Groth:** Writing – original draft. **Jakub Okrzeja:** Writing – original draft. **Adam Garkowski:** Formal analysis, Writing – original draft. **Wolfgang Kristoferitsch:** Investigation, Writing – review & editing, Supervision. **Alina Kułakowska:** Supervision, Writing – review & editing. **Joanna Zajkowska:** Investigation, Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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Supplementary materials

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References

Bogovic, P., 2015. Tick-borne encephalitis: a review of epidemiology, clinical characteristics, and management. World J. Clin. Cases 3 (5), 430. https://doi.org/10.12998/wjcc.v3.i5.430.

Bogovič, P., Lotrič-Furlan, S., Avšič-Županc, T., Lusa, L., Strle, F., 2018. Factors associated with severity of tick-borne encephalitis: a prospective observational study. Travel Med. Infect. Dis. 26, 25–31. https://doi.org/10.1016/J.TMAID.2018.10.003.

Caracciolo, I., Bassetti, M., Paladini, G., Luzzati, R., Santon, D., Merelli, M., de Sabbata, G., Carletti, T., Marcello, A., D'Agaro, P., 2015. Persistent viremia and urine shedding of tick-borne encephalitis virus in an infected immunosuppressed patient from a new epidemic cluster in North-Eastern Italy. J. Clin. Virol. 69, 48–51. https://doi.org/10.1016/J.JCV.2015.05.019.

Chmelík, V., Chrdle, A., Růžek, D., 2016. Fatal tick-borne encephalitis in an immunosuppressed 12-year-old patient. J. Clinical Virol. 74, 73–74. https://doi.org/10.1016/J.JCV.2015.11.029.

de Bruijn, M., van der Lely, N., Marcelis, J., Roks, G., 2015. ['Tick-borne' encephalitis in an immunocompromised patient]. Ned. Tijdschr. Geneeskd. 159. A9067. https://pubmed.ncbi.nlm.nih.gov/26648575/.

Elsterova, J., Palus, M., Sirmarova, J., Kopecky, J., Niller, H.H., Ruzek, D., 2017. Tick-borne encephalitis virus neutralization by high dose intravenous immunoglobulin. Ticks Tick Borne Dis. 8 (2), 253–258. https://doi.org/10.1016/J.TTBDIS.2016.11.007.

Grygorczuk, S., Świerzbińska, R., Kondrusik, M., Dunaj, J., Czupryna, P., Moniuszko, A., Siemieniako, A., Pancewicz, S., 2018. The intrathecal expression and pathogenetic role of Th17 cytokines and CXCR2-binding chemokines in tick-borne encephalitis. J Neuroinflammation 15 (1). https://doi.org/10.1186/S12974-018-1138-0.

Harpaz, R., Dahl, R.M., Dooling, K.L., 2016. Prevalence of immunosuppression among US adults, 2013. JAMA 316 (23), 2547–2548. https://doi.org/10.1001/JAMA.2016.16477.

Hertzell, K.B., Pauksens, K., Rombo, L., Knight, A., Vene, S., Askling, H.H., 2016. Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. Vaccine 34 (5), 650–655. https://doi.org/10.1016/j.vaccine.2015.12.029.

Holzmann, H., 2003. Diagnosis of tick-borne encephalitis. Vaccine 21 (SUPPL. 1), S36–S40. https://doi.org/10.1016/S0264-410X(02)00819-8.

Horger, M., Beck, R., Fenchel, M., Ernemann, U., Nägele, T., Brodoefel, H., Heckl, S., 2012. Imaging findings in tick-borne encephalitis with differential diagnostic considerations. 199(2), 420–427. doi:10.2214/AJR.11.7911.

Kaiser, R., 2012. Tick-borne encephalitis: clinical findings and prognosis in adults. Wiener Medizinische Wochenschrift 162 (11–12), 239–243. https://doi.org/10.1007/S10354-012-0105-0. *1946*.

Kaiser, R., Holzmann, H., 2000. Laboratory findings in tick-borne encephalitis–correlation with clinical outcome. Infection 28 (2), 78–84. https://doi.org/10.1007/S150100050051.

Knight, A., Pauksens, K., Nordmark, G., Kumlien, E., 2017. Fatal outcome of tick-borne encephalitis in two patients with rheumatic disease treated with rituximab. Rheumatology (Oxford) 56 (5), 855–856. https://doi.org/10.1093/RHEUMATOLOGY/KEW495.

Kuivanen, S., Smura, T., Rantanen, K., Kämppi, L., Kantonen, J., Kero, M., Jääskeläinen, A., Jääskeläinen, A.J., Sane, J., Myllykangas, L., Paetau, A., Vapalahti, O., 2018. Fatal tick-borne encephalitis virus infections caused by siberian and european subtypes, Finland, 2015. Emerging Infect. Dis. 24 (5), 946. https://doi.org/10.3201/EID2405.171986.

Lindquist, L., Vapalahti, O., 2008. Tick-borne encephalitis. Lancet 371 (9627), 1861–1871. https://doi.org/10.1016/S0140-6736(08)60800-4.

Lipowski, D., Popiel, M., Perlejewski, K., Nakamura, S., Bukowska-Ośko, I., Rzadkiewicz, E., Dzieciątkowski, T., Milecka, A., Wenski, W., Ciszek, M., Dêbska-Ślizień, A., Ignacak, E., Cortes, K.C., Pawełczyk, A., Horban, A., Radkowski, M., Laskus, T., 2017. A cluster of fatal tick-borne encephalitis virus infection in organ transplant setting. J. Infect. Dis. 215 (6), 896–901. https://doi.org/10.1093/INFDIS/JIX040.

Meneghini, M., Bestard, O., Grinyo, J.M., 2021. Immunosuppressive drugs modes of action. Best Practice Res. Clinical Gastroenterol. 54–55. https://doi.org/10.1016/J.BPG.2021.101757.

Pettersson, J.H.O., Golovljova, I., Vene, S., Jaenson, T.G.T., 2014. Prevalence of tick-borne encephalitis virus in Ixodes ricinus ticks in northern Europe with particular reference to Southern Sweden. Paras. Vectors 7 (1), 1–11. https://doi.org/10.1186/1756-3305-7-102/TABLES/1.

Rabel, P.O., Planitzer, C.B., Farcet, M.R., Kreil, T.R., 2012. Tick-borne encephalitis virus-neutralizing antibodies in different immunoglobulin preparations. Clinical Vaccine Immunology : CVI 19 (4), 623. https://doi.org/10.1128/CVI.05705-11.

Sadkowska-Todys, M., Zieliński, A., Czarkowski, M.P., 2020. Infectious diseases in Poland in 2018. Przegl. Epidemiol. 74 (4), 569–582. https://doi.org/10.32394/PE.74.49.

Sendi, P., Hirzel, C., Pfister, S., Ackermann-Gäumann, R., Grandgirard, D., Hewer, E., Nirkko, A.C., 2017. Fatal outcome of european tick-borne encephalitis after vaccine failure. Front Neurol 8, 119. https://doi.org/10.3389/FNEUR.2017.00119. APR.

Stefanoff, P., Rubikowska, B., Bratkowski, J., Ustrnul, Z., Vanwambeke, S.O., Rosinska, M., 2018. A Predictive Model Has Identified Tick-Borne Encephalitis High-Risk Areas in Regions Where No Cases Were Reported previously, Poland, 1999-2012. Int. J. Environ. Res. Public Health 15 (4). https://doi.org/10.3390/IJERPH15040677.

Stefanoff, P., Zielicka-Hardy, A., Hlebowicz, M., Konior, R., Lipowski, D., Szenborn, L., Siennicka, J., Orlikova, H., 2013. New endemic foci of tick-borne encephalitis (TBE) identified in districts where testing for TBE was not available before 2009 in Poland. Paras. Vectors 6 (1). https://doi.org/10.1186/1756-3305-6-180/METRICS.

Steininger, P.A., Bobinger, T., Dietrich, W., Lee, D.H., Knott, M., Bogdan, C., Korn, K., Lang, R., 2017. Two cases of severe tick-borne encephalitis in rituximab-treated patients in germany: implications for diagnosis and prevention. Open Forum Infect. Dis. 4 (4) https://doi.org/10.1093/OFID/OFX204.

Zajkowska, J., Czupryna, P., Pancewicz, S., Adamczyk-Przychodzeń, A., Kondrusik, M., Grygorczuk, S., Moniuszko, A., 2011. Fatal outcome of tick-borne encephalitis - a case series. Neurol. Neurochir. Pol. 45 (4), 402–406. Retrieved September 25, 2017, from. http://www.ncbi.nlm.nih.gov/pubmed/22102003.

Zawadzki, R., Garkowski, A., Kubas, B., Zajkowska, J., Hładuński, M., Jurgilewicz, D., Łebkowska, U., 2017. Evaluation of imaging methods in tick-borne encephalitis. Polish J. Radio. 82, 742. https://doi.org/10.12659/PJR.903940.