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Short communication

Severe tick-borne encephalitis in a patient recovered from COVID-19

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A B S T R A C T

North-eastern Poland is an endemic region for tick-borne encephalitis (TBE). The COVID-19 pandemic overlapped with the activity period of ticks that are the main vectors for TBE. As we know from short observation worldwide, SARS-CoV-2 virus affects significantly the immune system and can lead to serious complications of other infections even in previously healthy patients.

A 24-year-old female patient, who lived close to the forest, was admitted to the Department of Neurology at Medical University of Białystok with fever, dizziness, and progressive left-sided hemiparesis for three days. She had no medical history of chronic disease and was not vaccinated against TBE. The patient had SARS-CoV-2 infection three weeks prior to admission to the hospital (positive IgG against SARS-CoV-2). During COVID-19 infection she had fever, myalgia, a mild dysexecutive syndrome without indications for oxygen therapy and recovered after one week. During hospitalisation in the Department of Neurology the patient presented neck stiffness, progressing tetraparesis, dysthria and weakness of the neck muscles. The magnetic resonance imaging revealed a large, mainly in both thalamus, longitudinal lesion was found in the cervical spinal cord. The cerebrospinal fluid analysis indicated lymphocytic inflammation. A high level of TBE antibodies in both serum and CSF was found. After immunoglobulin and symptomatic treatment her condition gradually improved. The recovery after SARS-CoV-2 infection overlapping with TBE might have influenced the course of tick-borne disease in a bad manner. The correct diagnosis can be a challenge as COVID-19 can lead to further complications, also neurological. The co-incidence we observed is very rare, however during the pandemic it is pivotal to remember about possible occurrence of other infections and their atypical course.

1. Introduction

Tick-borne encephalitis (TBE) is an infectious disease of the central nervous system caused by a virus belonging to the family of Flaviviridae. Five subtypes of this pathogen are mainly responsible for most cases: (1) European, (2) Far-eastern and (3) Siberian and the newly identified (4) Baikalian subtype, (5) and Himalayan subtype (Boucher et al., 2017; Deviatkin et al., 2020). The virus is usually transmitted by ticks, occasionally by drinking contaminated unpasteurized milk. The patchy endemic foci of the disease are found all over Europe and Asia. Studies show an increase in the incidence of TBE and spread of endemic areas to new regions, probably due to climate changes and more outdoor leisure activities. Currently most cases are found in Central Europe, the Baltic Region, Russia, and Eastern Asia (Riccardi et al., 2019). TBE is one of the most common viral infections of the central nervous system in Poland. North-eastern Poland is an endemic area with an incidence of 6.17 cases/100,000 persons/year (Kuchar et al., 2021).

The disease usually presents with a biphasic course. The first viremic phase is mild and nonspecific (fever, headache, myalgia, fatigue) and lasts for about a week. In majority of symptomatic cases, the disease resolves at this point. However, in some individuals, another more severe phase follows. The clinical manifestation of the second phase varies from mild aseptic meningitis to severe meningoencephalitis accompanied by myelitis and acute flaccid paralysis with a fatal outcome (Kaiser, 2008). Severe cases are usually seen in immunocompromised individuals (de Bruijn et al., 2015).

The pandemic of Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) overlapped with the activity period of Ixodes ricinus ticks, the main vector for TBE in Europe. As we know from the short period of worldwide observations, the SARS-CoV-2 virus significantly affects the immune system and can lead to serious complications during the course of other
infections even in previously healthy patients (Kuchar et al., 2021). Although the virus targets mainly the respiratory track, accompanying neurological symptoms are common. Most often reported symptoms include: headache, olfactory dysfunction, encephalopathy, encephalitis and cerebrovascular pathologies, acute myelitis, and Guillain-Barre syndrome (Yachou et al., 2020; Lechien et al., 2020). It is not clear if the reported symptoms are induced by the virus or triggered by a chain of immune reactions. Studies show that the nervous system presumably can be affected in multiple ways, both directly and for the most part indirectly (Fotuhi et al., 2020; Kumar et al., 2020).

2. Case report

A 24-year-old female patient with no medical history of chronic diseases was admitted to the Department of Neurology at Medical University of Białystok in early December of 2020 with fever, dizziness, and progressive left-sided hemiparesis for the last three days. She lived in north-eastern Poland, close to the forest, owned a dog, and had recreationally been picking mushrooms. She did not report a recent tick bite and was not vaccinated against TBE. The patient had a SARS-CoV2 infection three weeks prior to admission to the hospital (as shown by positive IgG against SARS-CoV-2 at admission; performed tests: Diasorin Liaison® SARS-COV-2 S1/S2 IgG, Diasorin Liaison® SARS-COV-2 IgM). During the COVID-19 infection she had fever, myalgia, and mild dyspnœa (without indications for oxygen therapy) and recovered after one week. In the Department of Neurology, the patient presented the following symptoms: neck stiffness, signs of the lower motor neuron weakness in the upper limb, and upper motor neuron weakness in the lower limb more dominant on the left side (left limbs grade 2 and right limbs grade 3 in the Medical Research Council Scale for Muscle Strength), dysarthria, and right six cranial nerve palsy. Her clinical condition deteriorated rapidly during the first week of hospitalization, weakness increased to left limbs grade 1 and right limb grade 2 on the MRC scale and head droop appeared due to weakness of the neck muscles. The magnetic resonance image (MRI) of the head revealed numerous unspecific lesions, mainly in the thalamus, hyperintense on T2-weighted (T2) and fluid-attenuated inversion recovery (FLAIR) images, and similar lesions were presented in both cerebellar hemispheres (Fig. 1). What is more, the MRI of the head in axial contrast-enhanced T1-weighted subtraction maps revealed moderate bilateral, mixed pachymeningeal and leptomeningeal contrast enhancement in in selected regions (Fig. 2). On the MRI of cervical spinal cord, a longitudinal lesion was found with hyperintense on T2 and short tau inversion recovery (STIR) sequences (Fig. 3). No abnormalities were found on brain computer tomography angiography scans. Blood inflammatory parameters were slightly elevated. The cerebrospinal fluid analysis showed lymphocytic pleocytosis (Table 1). High levels of IgM and IgG TBE antibodies in serum and in CSF were found (performed with: TBE IgG/IgM ELISA for serum and CSF, VIROTECH Diagnostics GmbH). The results led to the diagnosis of TBE. However, due to the fact that the analysis took several days to complete, a wide differential diagnostics was made simultaneously, which allowed us to exclude other possible neuro-infections. The cerebrospinal fluid was tested with polymerase chain reaction (PCR) with a negative result for Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Cytomegalovirus, Enterovirus, Herpes simplex viruses 1 and 2, Human herpesvirus 6, Human parvovirus, Varicella zoster virus, and Cryptococcus neoformans/gattii. Testing for the presence of Borrelia burgdorferi in serum and cerebrospinal fluid (CSF) showed negative results. Microbiological testing on bacterial cultures from blood and CSF were negative. In addition, diagnostic tests for autoimmune diseases were performed, i.e. Neuromyelitis optica spectrum disorders (NMOSD). Tests for presence of anti-aquaporin-4 antibody (AQP4-Ab), antibodies to myelin oligodendrocyte glycoprotein (anti-MOG), and myelin basic protein antibodies (anti-MBP) were negative. We performed two electromyographic examinations which did not show any pathological changes of motor and sensory nerves compatible with demyelinating and axonal dysfunction. Further research excluded connective tissue diseases and paraneoplastic syndromes. The serum was negative for rheumatoid factor, anti-prothrombin, antiphospholipid, and anti-neutrophil cytoplasmic antibodies and antigens against dsDNA, nucleosome, histosome, SS-A, Ro-

Fig. 1. Initial MRI of the brain of a 24-year-old woman diagnosed with TBE. Axial FLAIR (A,D,E), axial T2-weighted (B,F) and coronal T2-weighted images (C) depict: bilaterally quite symmetric hyperintense areas in the thalami (white arrows) and the posterior putamina (yellow arrows), bilateral and symmetric hyperintense signal at the midbrain, sparing the red nucleus and substantia nigra (yellow asterix) (C), hyperintense signal in the dorsal pons (red arrows) and within cerebellar vermis (white asterix), and also several cortical-subcortical/leptomeningeal hyperintensities involving cerebellum cortex bilaterally (blue arrows). The last image (F) show bilateral symmetric hyperintense signal at the level of the junction of medulla and spinal cord (green arrows). These lesions did not demonstrate restricted diffusion on DWI/ADC sequences (not shown).
Table 1. Results of laboratory tests in reported cases

Based on the initial symptoms, the patient was empirically treated with antibiotic (ceftriaxone; Biotraxon Polpharma) and antiviral agents (acyclovir; Aciclovir Jelfa). Due to her severe clinical condition, extensive changes in the brain and longitudinal in the spinal cord, and rapid progression of symptoms, the patient was treated with an IgG infusion (OCTAGAM 10%, total dose of 120 g given for four days in equally divided doses). Anti-oedematous agents and other symptomatic treatment (pain killers, anxiolytics) were also used. During hospitalization,
the patient’s clinical condition stabilized and began to gradually improve.

The patient was transferred to the neurological rehabilitation department. Her neurological condition improved gradually; however, after several months of rehabilitation, a significant neurological deficit remained. She could maintain her head position and had no problems with swallowing but required assistance while walking due to limb weakness and massive muscle atrophy, especially in the shoulder girdle. On the control MRI performed after 6 months, a complete resolution of the previously seen signal alteration within the cerebrum, cerebellum and spinal cord lesions was seen (Fig. 4).

### Table 1

Results of laboratory tests of serum and CSF in the reported case. Most significant findings were: lymphocytic pleocytosis in CSF; high levels of IgM and IgG TBE antibodies in CSF.

| Test                  | Value              |
|-----------------------|--------------------|
| Serum TBE IgM         | 3.65 U/mL          |
| Serum TBE IgG         | 5.50 U/mL          |
| CSF TBE IgM           | > 100 U/mL (positive) |
| CSF TBE IgG           | 70.96 U/mL (positive) |
| CSF Color and transparency | aqueous, clear |
| Pleocytosis [c/mm³]   | 94                 |
| Lymphocytes [%]       | 64                 |
| Monocytes [%]         | 9                  |
| Macrophages [%]       | 1                  |
| Neutrophiles [%]      | 26                 |
| Glucose [mg/dl]       | 79                 |
| Protein [mg/dl]       | 189 (normal range 15–45) |
| Nonne-Apel test       | (–)                |
| Q Albumine ratio (CSF/plasma) | 0.032 |

3. Discussion

Usually TBE virus infection is mild or asymptomatic although severe encephalitis can occur. Bacterial co-infection increases the risk of a complicated clinical course of the infection. In the report of Zajkowska et al. (2011) of four fatal cases due to TBE, one was complicated by L. monocytogenes co-infection. Sometimes concomitant infection with B. burgdorferi sensu lato occurs, which may impact the course of the infection (Oksi et al., 1993). Mostly immunosuppressant treatments affect the frequency of infections, especially viral ones Steininger et al. (2017). reported two cases of severe TBE in patients who were undergoing rituximab treatment. The patient we presented had no comorbid diseases, and the only potential factor modifying the patient’s immunological condition was the prior SARS-CoV-2 infection.

The pattern of lesions, involving thalamus, cerebellum and spinal cord, were previously described in TBE (Horger et al., 2012). In the presented case, the MRI also revealed cerebellar leptomeningeal enhancement, reported in some severe TBE cases (Iff et al., 2005; Zawadzki et al., 2017). The involvement of the anterior part of the spinal cord can be longitudinal and need very careful differential diagnosis (e.g. autoimmune disorders) (Bender et al., 2005).

No targeted treatment against TBE virus infection exists. Although an effective vaccine is available, the vaccination rate is low in some endemic countries, including Poland (Erber and Schmitt, 2018). What is more, immunocompromised/immunosuppressed patients and those with some comorbid diseases cannot fully respond to vaccination against TBE (Sendi et al., 2017). In the presented case the used treatment was empirical. The decision to use IgG treatment was made due to rapid deterioration of the patient’s neurological condition and extensive changes on the MRI. The decision was made before TBE was proved and autoimmune origin after COVID-19 could not be excluded.

![Fig. 4](image-url)

**Fig. 4.** Final follow-up MRI performed within 6 months in other MRI unit (Bioskaner UMB). Axial T2 color-coded white matter fiber tractography (A–D) at the levels of previously affected areas show intact white matter tracts. Coronal 3D-FLAIR (E), sagittal STIR and T2-weighted images and axial T2-weighted images (F) demonstrate complete resolution of the previously seen signal alteration within cerebrum, cerebellum and spinal cord.
4. Conclusion

The recovery after SARS-CoV-2 infection overlapping with TBE might have influenced the course of tick-borne disease in a negative way. The correct diagnosis can be a challenge as COVID-19 can lead to further complications, also neurological. The co-incidence we observed is very rare, however during the pandemic it is pivotal to remember about possible occurrence of other infections and their atypical course. In endemic areas prophylactic vaccinations against TBE virus are strongly recommended.

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.

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References

Bender, A., Schulte-Altedorneburg, G., Walthier, E.U., Pfister, H-W., 2005. Severe tick-borne encephalitis with simultaneous brain stem, bithalamic, and spinal cord involvement documented by MRI. J. Neurol. Neurosurg. Psychiatry 76, 135–137. https://doi.org/10.1136/jnnp.2004.040469.

Boucher, A., Herrmann, J.L., Morand, P., Buzel, P., 2015. Tick-borne encephalitis in an immunocompromised patient. Ned. Tijdschr. Geneeskd. 159, A9067.

Deviatkin, A.A., Karganov, G.G., Vakulenko, Y.A., Lukashev, A.N., 2020. TBEV subtyping in terms of genetic distance. Viruses 12, 1240. https://doi.org/10.3390/v12111240.

Erber, W., Schmitt, H.J., 2017. Evaluation of imaging methods in tick-borne encephalitis. Pol. J. Radiol. 82, 742–747. https://doi.org/10.12659/PJR.903940.

Fotuhi, M., Mian, A., Meyami, S., Raji, C.A., 2020. Neurobiology of COVID-19. J. Alzheimers. Dis. 76, 3–19. https://doi.org/10.3231/JAD-200581.

Horger, M, Beck, R, Fenchel, M, Ernemann, U, Nägele, T, Brodofel, H, Heckl, S., 2012. Imaging findings in tick-borne encephalitis with differential diagnostic considerations. AJR Am. J. Roentgenol. 199, 420–427. https://doi.org/10.2214/ AJR.11.7911. PMID: 22826407.

Iff, T, Meier, R, Olah, E, Schneider, JF, Tibussek, D, Berger, C, 2005. Tick-borne meningitis in a 6-week-old infant. Eur. J. Pediatr. 164, 787–788. https://doi.org/10.1007/s00431-005-1753-5. Epub 2005 Aug 20. PMID: 16133234.

Kaiser, R., 2008. Tick-borne encephalitis. Infect. Dis. Clin. North Am. 22, 561–575. https://doi.org/10.1016/j.ocl.2008.03.013.

Kuchar, E., Zajkowska, J., Fiszak, R., Mastalerz-Migas, A., Rosińska, M., Zajkowski, J., Widowik, P., Watusiak-Skorupka, J., 2021. Epidemiology, diagnosis, and prevention of tick-borne encephalitis in Poland and selected European countries – a position statement of the Polish group of experts. Med. Pr. 72, 193–210. https://doi.org/10.13075/mp.5893.01063.

Kumar, A, Pareek, V, Praoon, F, Ma, Kumar, P, Kumari, C, Narayan, RK., 2020. Possible routes of SARS-CoV-2 invasion in brain: in context of neurological symptoms in COVID-19 patients. J. Neuosci. Res. 98, 2376–2383. https://doi.org/10.1002/jnr.24717.

Lechien, J.R., Chiessa-Estomba, C.M., et al., 2020. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur. Arch. Otorhinolaryngol. 277, 2251–2261. https://doi.org/10.1007/s00431-020-05965-1.

Ohki, J., Viljanen, M.K., Kalimo, H., Peltonen, R., Marttila, R., Salomaa, P., Nikoskelainen, J., Budka, H., Halonen, P., 1993. Fatal encephalitis caused by concomitant infection with tick-borne encephalitis virus and Borrelia burgdorferi. Clin. Infect. Dis. 16, 392–396. https://doi.org/10.1093/CLINID/16.3.392.

Riccardini, N., Antonello, R.M., Luzzati, R., Zajkowska, J., Di Bella, S., Giacobbe, D.R., 2019. Tick-borne encephalitis in Europe: a brief update on epidemiology, diagnosis, prevention, and treatment. Eur. J. Intern. Med. 62, P1–P6. https://doi.org/10.1016/j.ejim.2019.01.004.

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.

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. https://doi.org/10.1093/ofid/ofx204. Dis. 4.

Yachou, Y., El IdriSSI, A., Belapasov, V., Ait Benali, S., 2020. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neur. Sci. 41, 2657–2669. https://doi.org/10.1007/s10072-020-04575-3.

Zajkowska, J., Grzywna, P., Panczewicz, S., Adamczyk-Przychodzen, A., Kondrusik, M., Grygorczuk, S., Moniuszko, A., 2011. Zgon w przebiegu kleszczowego zapalenia mózgu - opis serii przypadków. [Fatal outcome of tick-borne encephalitis – a case series] Neurol. Neurochir. Pol. 45, 402–406. https://doi.org/10.5603/NNP.a718.

Zawadzki, R., Garkowski, A., Kubas, B., Zajkowska, J., Hladunski, M., Jurczykiewicz, D., Lebokowska, U., 2017. Evaluation of imaging methods in tick-borne encephalitis. Pol. J. Radiol. 82, 742–747. https://doi.org/10.12659/PJR.903940.