Case Report

Tick-borne Encephalitis: Stroke-like Presentation

Andreas Eleftheriou, MD,*'‡ Fredrik Lundin, PhD, MD,*'‡ and Evangelos Alexandros Petropoulos, MD†

Tick-borne encephalitis, caused by the tick-borne virus (TBEV), is endemic in central, eastern, and northern Europe eastwards through Russian Siberia and China. For the year 2009, the highest incidence in Scandinavian countries was in Sweden. The clinical symptoms have a wide spectrum. We report a unique case of clinical symptoms and radiological findings compatible with a stroke-like inflammatory lesion in the thalamus, suggesting microangiopathy from TBEV. Our case shows that TBEV could be a possible cause of stroke-like lesions.

Key Words: Tick-borne encephalitis—thalamus—cerebral infarction—cerebrovascular disease—DWI—ADC

Introduction

Tick-borne virus is an arthropod-borne virus, belonging to the family Flaviviridae,[1] genus flavivirus[2] and called tick-borne virus (TBEV) sensu lato, and occurs in humans after a bite from an infected tick. In recent years, the range of TBEV distribution has been growing, especially in north-western Europe. This phenomenon is associated with global warming, leading to increased activity of ticks.[3] Tick-borne encephalitis (TBE) is endemic in central, eastern, and northern Europe eastwards through Russian Siberia and China.[4] According to data for the year 2009 for the countries of Scandinavia, Sweden had the highest incidence for TBE (2.3 per 100 000).[5] The majority of infections are either asymptomatic or symptomatic with febrile illness. The first viraemic phase is symptom-free and varies from 1 to 33 days.[6] During the second phase in severe cases, the TBEV infects the central nervous system (CNS), resulting in viral meningitis or encephalomyelitis[7] but the pathogenetic mechanisms which can explain the invasion pathway in the CNS are uncertain.[8] TBE is a potentially fatal disease syndrome of humans and some other mammals.[9] Antibodies in blood and cerebrospinal fluid (CSF) can be detected by serological tests. In infected infant rats, viral antigens presented in different brain regions, including the cerebellum, midbrain, hippocampus, thalamus, and frontal pole.[10] The clinical symptoms described in the literature have a wide spectrum such as high fever, headache, nausea, vertigo, loss of consciousness ranging from somnolence to stupor, convulsions, speech disorders, delirium, diplopia, impaired hearing, bulbar palsy, paresis limb hyperkinesias, ataxia, and sensory symptoms.[11,12]

We report a unique case where the patient developed symptoms compatible with a stroke-like inflammatory lesion in the left thalamus, presumably caused by TBEV.

List of Abbreviations used: TBE, tick-borne encephalitis; TBEV, tick-borne virus; CNS, central nervous system; BPM, beats per minute; CRP, c - reactive protein; CT, computer tomography; LP, lumbar puncture; ER, emergency department; CSF, cerebrospinal fluid; MRI, magnet resonance imaging; TOF, time of flight angiography; VIEU, VIENNA units; FLAIR, T2-weighted-fluid-attented inversion recovery; DWI, diffusion-weighted magnetic-resonance imaging; ADC, apparent diffusion coefficient; TLR3, toll-like receptor 3; dsRNA, double-stranded ribonucleic acid; NK, natural killers; CCR5, C-C chemokine receptor type 5; IgG, immunoglobulin

From the *Department of Neurology, and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; †Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden; and ‡Department of Neurology, University Hospital, Linköping, Sweden.

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Address correspondence to Andreas Eleftheriou, MD, Department of Neurology, University Hospital, Garnisonsvägen 10, 58750 Linköping, Sweden. E-mails: andelef2002@yahoo.gr, Andreas.eleftheriou@regionostergotland.se.

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Case Report

A 64-year-old male with hypertension but otherwise previously healthy presented at the emergency department with fever (up to 38.5°C) that had lasted about 10 days and malaise and fatigue that had occurred during the last week. Two days previously he experienced a temporary improvement, but was currently suffering from headache and progressive monoparesis in the lower right extremity. In the global examination the patient appeared in normal general condition. His body temperature was 37.4°C, his skin was without rash, lung and heart auscultation were normal with a respiratory rate of 24, saturation 97% on air, blood pressure of 168/80 mm Hg, and pulse of 70 bpm.

In the neurological examination the patient was alert oriented, without neck stiffness, and had normal cranial nerve function. The right leg was slightly paretic with difficulty in walking and there was hyperreflexia of the right patella but Babinskiś sign was absent. There were no sensory abnormalities.

From blood investigation we noticed slight thrombocytopenia, lymphopenia, and elevated transaminases, CRP <10 mg/L.

A lung X-ray, an acute ultrasound of the liver and pancreas, and a computer tomography scan of the brain were normal. Clinically, the suspicion of meningitis seemed to be weak but the progressive monoparesis and patellar hyperreflexia in combination with a period of febrility were regarded as an indication of a lumbar puncture (LP). Unfortunately, there were technical problems with the LP in the emergency room and the patient was admitted to the neurology department. Further blood tests for *borrelia* and TBE serology were made. He had not been vaccinated against TBEV, something which is common for our hospital catchment area.

The next day the patient was still without fever but he had deteriorated in his neurological status. A new examination showed right-sided mild hearing loss, dysmetria with the finger-nose test, biceps hyperreflexia, allodynia of the right upper arm, lower right distal power, hyperreflexia of the right quadriceps, and difficulty in walking due to right leg weakness.

An LP showed pleocytosis with polymorphonuclear dominance (total leukocytes 554 × 10 6/L, poly 478 × 10 6/L) and a light barrier injury with CSF-albumin at 536 mg/L (<420 mg/L). The patient was given Acyclovir, Meropenem, and corticosteroids intravenously.

On the third day after admission the symptoms worsened, and dysarthria developed.

A magnet resonance imaging of the brain showed a hyperintense diffusion-weighted magnetic resonance imaging (DWI) lesion associated with elevated apparent diffusion coefficient (ADC) in the left thalamus, consistent with inflammation or subacute infarction. In addition, there were chronic ischaemic changes in the periventricular areas and a chronic infarction in the left internal capsule (Fig 1). MR-time of flight angiography showed normal arteries. Cytomegalovirus, Epstein Barr virus (VCA immunoglobulin M [IgM]), and Brucella were negative for IgM. Both IgG and IgM in CSF and blood were negative for borreliosis. First TBE blood serology, done with Enzygnost ELISA (Siemens, Germany), was positive for IgM (358.34 VIEU/mL) (cut-off 63-126 VIEU/mL) negative for IgG (57.30 VIEU/mL)(cut-off 63-126 VIEU/mL) (VIEU means VIENNA Units). The treatment

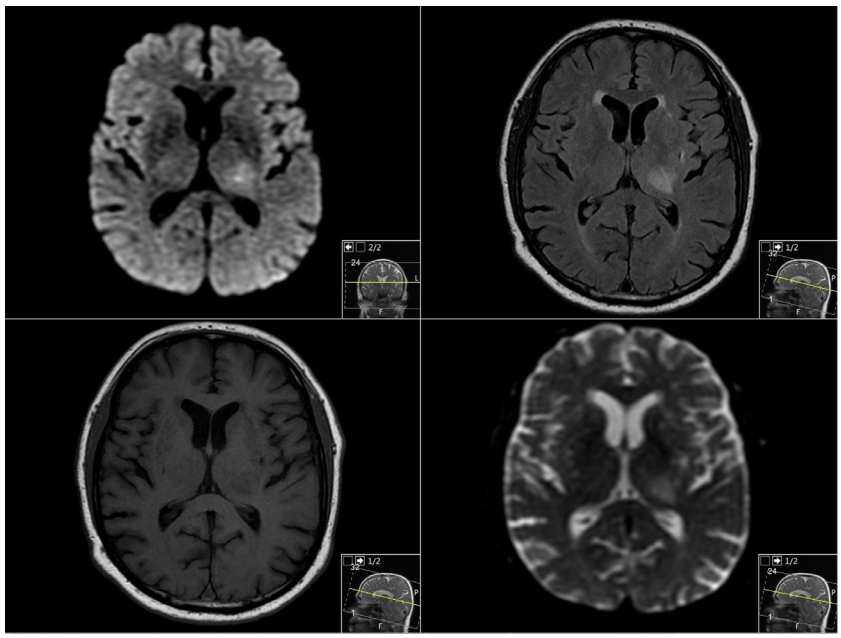

Figure 1. *A brain MRI showed a hyperintense DWI lesion associated with elevated ADC in the left thalamus, consistent with inflammation or subacute infarction. In addition, there were chronic ischaemic changes in the periventricular areas and a chronic infarction in the left internal capsule.*

with acyclovir and meropenem was stopped. The entire disease picture was regarded as a possible TBEV-triggered micro-angiopathy. An echocardiogram showed sinus rhythm and there were no abnormalities on ultrasound of the heart and carotid vessels and thus no sign of thromboembolism. Second TBE serology 1 month after the first was positive for IgM and IgG.

After 26 days in the neurology department the patient was discharged. At that time the patient had permanent weakness in the right arm and leg. After rehabilitation the patient was improved and at a clinical control 2 months after discharge he used a walker, but dysarthria and hearing problems had resumed.

The TBE diagnosis was confirmed by convalescent samples that showed positive IgM (150.89 VIEU/mL)(cut-off 63-126 VIEU/mL) and IgG (>650 VIEU/mL)(cut-off 63-126 VIEU/mL) for TBE in the blood.

Discussion

The pathogenetic mechanism which can explain the invasion of TBEV in the CNS is uncertain. A case of TBE is defined by the presence of clinical signs of meningitis, meningoencephalitis or meningoencephalomyelitis with CSF pleocytosis ($>5 \times 106$ cells/L), and the presence of specific TBEV serum IgM and IgG antibodies, CSF IgM antibodies, or TBEV IgG seroconversion.[12] In our patient, the diagnosis of TBE is confirmed by the clinical picture in combination with specific antibodies and finding evidence of brain inflammation in the CSF. It is of high interest that the patient suffered from slight thrombocytopenia and lymphopenia which are typical features in patients with TBE infection.

The patient developed his neurological symptoms slowly. An acute brain computer tomography of the brain performed at the emergency room showed no signs which could suggest acute cerebrovascular disease or oedema. Because of clinical worsening and permanent paresis the investigation was completed with an MR of the brain at 1.5 Tesla. Using the T2-weighted fluid-attenuated inversion recovery protocol, we noticed the presence of hyperintensity in the left thalamus area with influence on the internal capsule which was consistent with a focal lesion, but further explanation was not possible.[13] DWI together with qualitative and quantitative assessment of the ADC are particularly sensitive to detection of acute ischaemic stroke within a few minutes after arterial occlusion and to differentiation of acute stroke from other processes that manifest with sudden neurologic deficits.[14,15] Nonetheless, encephalitis lesions in an acute or subacute phase could also cause hyperintensity on DWI with associated decreased ADC. However, DWI hyperintensity varies in patients with vasogenic oedema and is combined with increased ADC.[16] Furthermore, in patients with inflammatory brain diseases, myelin oedema or cytotoxic oedema could decrease water movement in the extracellular space which could cause a decreased ADC and can mimic an infarction.[17] In our case there was hyperintensity in DWI and subsequent increased sign in the ADC. The radiological picture was described by our radiologists could be compatible with a subacute stroke-like lesion. With the use of MR-time of flight angiography there were no signs for abnormal arteries.

The whole cardiovascular investigation was clear and there was no elevation of erythrocyte sedimentation. Our patient suffered a possible subacute stroke-like lesion during or because of a TBE infection.

As we know TBEV causes an inflammatory reaction in the CNS with subsequent cell dysfunction. As the virus spreads into the CNS through the endothelium of the vessel, this causes, initially, focal degeneration and necrosis, and then the development of inflammatory infiltrates both focally and perivascular with a toll-like receptor 3 mediated process.[18] toll-like receptor 3 is expressed on dendritic cells, astrocytes, microglia, oligodendrocytes, Schwann cells, and epithelium. Viral antigen has been detected in large neurons in patients with TBE. Hence, it is not possible to find a clear explanation of why our patient developed suspect stroke-like lesion during TBE infection.

Our case shows that TBEV could be a cause of possible stoke-like lesion, possibly from inflammatory micro-angiopathy. Nonetheless, coincidental small-vessel infarction from underlying lipohyalinosis or microatheroma cannot be excluded given the patient's age and history of hypertension. The case did not have the typical meningoencephalic presentation expected in CNS viral infections. The patient has developed permanent right low extremity weakness that significantly affects his quality of life.

The case draws attention to the assessment of patients with unclear acute focal neurological symptoms, especially if the increasing incidence of TBE is considered.

Declarations

Ethics approval and consent to participate: There is no need for ethics approval.

Consent for publication: The authors have the signed consent to publish this case from the patient. The consent has been signed 14 May, 2018. The patient understood that the information would be published without his/her name attached, but that full anonymity could not be guaranteed. The patient understood that the text and any pictures or videos published in the article would be freely available on the internet and may be seen by the general public. The pictures, videos, and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes. The patient has been offered the opportunity to read the manuscript.

Availability of data and material: We used the data from our Cambio COSMIC Healthcare System, which is a digital comprehensive healthcare system installed in all clinics in our region.

Authors' Contributions

Andreas Eleftheriou and Fredrik Lundin were the neurologists who performed the neurological investigation. Andreas Eleftheriou was the major contributor in writing the manuscript. Alexandros Evangelos Petropoulos was working for the Infection Clinic of our hospital during that period, he performed the infection investigation at the beginning of patients illness. All authors read and approved the final manuscript.

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