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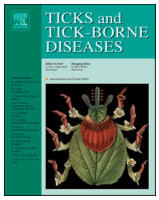

Tick-borne encephalitis as a trigger for anti-*N*-Methyl-D-aspartate receptor encephalitis

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ABSTRACT

Tick Borne Encephalitis (TBE) is endemic to an increasing number of countries and is a common cause of meningoencephalitis in Europe and Asia making any potential complications of the disease increasingly relevant to clinicians.

We present, what is to our knowledge, the second reported case of *N*-methyl-d-aspartate receptor (NMDAR) encephalitis following Tick Borne Encephalitis (TBE) in a 47-year-old Lithuanian man. The case provides further evidence of TBE being a possible trigger of NMDAR encephalitis and highlights the importance of being aware of symptoms of autoimmune encephalitis in patients with infectious encephalitis.

1. Introduction

Tick Borne Encephalitis (TBE) is an infection caused by several viruses of the *Flaviviridae* family transmitted by tick-bite from ticks of the *Ixodes spp*. Clinically it is characterized by a biphasic illness with initial symptom onset a median eight days after exposure with fever, malaise and fatigue followed by neurological manifestations in up to a third of patients including meningitis and encephalitis of varying degrees of severity (Beauté et al., 2018). The incidence of TBE is on the rise and geographical dissemination of the disease vector has caused TBE to become endemic in an increasing number of countries, a phenomenon to which manmade climate change is thought to be a major contributing factor (Johnson et al., 2023; Wondim et al., 2022).

1.1. Clinical case description

A 47-year-old Lithuanian man employed as a truck driver passing through Denmark was admitted to the emergency department with confusion, headache, ataxia and agitation. The patient was found in this state by his colleagues and according to his niece, who was contacted by telephone, he had become increasingly confused with trouble ambulating for the last two days. According to the patient the headache had started a week prior to admission but he was unable to provide any further history. The patient was apyrexial with moderately elevated inflammatory markers (White blood cell count 11,8 10^9/L, CRP 60 mg/L). As a result of severe agitation the patient was sedated and transferred to the intensive care unit.

According to family members the patient suffered from mild hypertension and occasionally used benzodiazepines, for which the indication remained uncertain. Otherwise he was healthy with no history of substance abuse.

The patient was reported to have had a three week history of abdominal pain, fever and malaise and had sustained a tick bite in Lithuania four weeks prior to admission.

A lumbar puncture showed clear CSF with a white cell count of 480 WBC/mm^3 (290 lymphocytes), slightly elevated protein 0,8 g/L and a glucose level of 2,8 mmol/L (blood glucose 5,2 mmol/l). C-X-C Motif Chemokine Ligand 13 (CXCL13) was elevated (104 ng/L). No oligoclonal bands were detected.

A tentative diagnosis of viral encephalitis was established based on the clinical presentation and antiviral treatment with Acyclovir was initiated accordingly.

CSF PCR testing was negative for Herpes simplex virus type 1 and 2, varicella-zoster virus, enterovirus, Epstein-Barr virus and tuberculosis.

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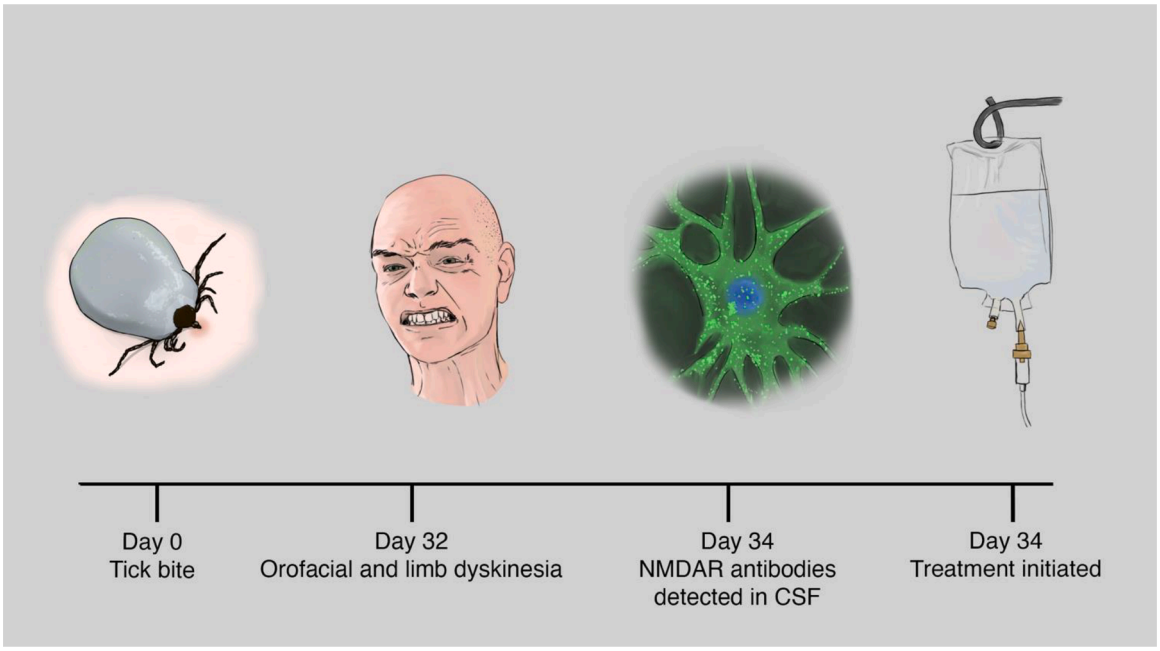

Fig. 1. Timeline of events
A 47-year-old man sustained a tick bite and developed encephalopathy and agitation four weeks later, he tested positive for antibodies against Tick Borne Encephalitis. Thirty-two days after the initial tick bite he developed orofacial and limb dyskinesia and two days later NMDAR antibodies were detected in CSF and serum and treatment was started with intravenous steroids later that day.

Testing for Borrelia IgG and IgM antibodies in both serum and CSF was negative. Serological testing for HIV, syphilis and tuberculosis as well as a drug screening was also negative. CSF microbial testing did not detect any microorganisms.

MRI of the brain and spinal cord was unremarkable.

Upon removal of sedation five days after admission, he was still confused and slightly agitated and had developed orofacial dyskinesia as well as dyskinesia of the left arm suggestive of anti-NMDAR encephalitis. At this point the TBE serological analysis had not yet been completed and a second lumbar puncture was performed on suspicion of autoimmune encephalitis. The second lumbar puncture revealed a white blood cell count at 380 (all lymphocytes) and markedly elevated protein 1,25 g/L with a glucose level of 3.1 mmol/L. Again, no oligoclonal bands were detected. Anti-neural surface antibodies were tested for with indirect immunofluorescence using commercial fixed cell-based assays transfected with the following antigens: NMDAR NR1 subunit, GAD65, LGI1, CASPR2, AMPAR1, AMPAR2, GABAb receptor B1/B2, IgLON5, DPPX and GABAa receptor (Euroimmun, Lübeck, Germany) (Uy et al., 2021). Anti-NMDAR antibodies were moderately positive in CSF (titer 1:3.2) and strongly positive in serum (titer 1:1000).1000.

After the second lumbar puncture was performed, the results of serological testing (Serion scion ELISA assay kit) for TBE antibodies on serum, taken at the time of admission, returned positive for TBE IgG with a titer of 475,5 U/mL (normal cut-off: 150 U/mL) and IgM with a titer of 144,8 U/mL (normal cut-off: 15 U/mL), indicative of recent infection. TBE IgM testing was performed on CSF from the second lumbar puncture, which was positive with a titer of 127,3 U/ml (normal cut-off value of 15 U/mL). Based on the history, clinical features and ancillary testing, the patient was diagnosed with post-viral NMDAR encephalitis secondary to TBE. He was transferred to the neurological department and treatment with a five day course of high dose intravenous steroids (1 gram per day) was initiated. For a graphical presentation of the timeline see Fig. 1.

Upon this treatment the patient improved markedly with complete remission of confusion and dyskinesia and a peroral prednisolone taper was initiated. The patient was transferred to a Lithuanian hospital for continued treatment and rehabilitation.

2. Discussion

Based on the clinical presentation with orofacial dyskinesia and upper limb dystonia with onset four weeks after a tick bite in combination with serological findings we find it likely that this case is an NMDAR encephalitis following TBE. We consider this case significant for several reasons. Firstly it reaffirms the validity of the previously published case report of anti-NMDAR encephalitis following TBE (Cavaliere et al., 2019). Furthermore post-herpetic autoimmune encephalitis is a well-known entity, but there are now reports of other viruses causing subsequent anti-NMDAR encephalitis including Japanese encephalitis (JE), which, like TBE, is a flavivirus (Cavaliere et al., 2019; Nibber et al., 2014). Activation of NMDAR plays a central part in the neuronal inflammation induced by Japanese encephalitis, which hints at a possible mechanism for induction of autoimmune encephalitis (Chen et al., 2018). A previous study of 20 children with post-JE infection NMDAR encephalitis found that the median time elapsed from the first symptom of JE-virus infection to NMDAR encephalitis diagnosis was 29 days (range 16–51 days) (Luo et al., 2022). Further, the time from TBE onset to onset of NMDAR encephalitis was reported as being one month in the only previously published case on the subject (Cavaliere et al., 2019). In our case, time from TBE onset to NMDAR diagnosis was approximately 26 days, which we deem to be in line with the aforementioned findings. Information regarding TBE vaccination status in our patient is not available. Breakthrough infections are usually more severe with greater need for ICU admission and more frequent and extensive MRI changes (Lotrič-Furlan et al., 2017; Wagner et al., 2020). In the event of a breakthrough TBE infection, diagnosis should be confirmed by demonstrating a rise in TBE IgG levels, an increased specific antibody index in the CSF or the presence of antibodies against the NS1 protein, which had not been done in our case (Albinsson et al., 2018; Pustijanac et al., 2023). A PET/CT scan of the body was not performed in order to rule out an underlying malignancy as an alternative etiology of the NMDAR encephalitis. In women between 18 and 35 years of age, the risk of NMDAR encephalitis being a paraneoplastic syndrome is between 35 and 50 %, while the risk is much lower in children and young men and malignancy occurs almost exclusively in

elderly patients of this population (Graus et al., 2021). In a retrospective cohort of NMDAR patients from 2009 to 2019 from our research group, we found an underlying tumor, other than ovarian teratoma, in 5 % of patients ($n = 55$) and only in patients aged 60 and above (Nissen et al., 2022). Further, the fact that the patient responded so well to treatment with intravenous steroids alone is highly unusual for patients with paraneoplastic NMDAR encephalitis. We find it very unlikely that the autoimmune encephalitis in this case is paraneoplastic, although an underlying cancer cannot be excluded completely without proper diagnostic workup.

3. Conclusion

Clinicians should bear in mind the possibility of secondary autoimmune encephalitis when treating patients with unusual manifestations of non-herpetic infectious encephalitis, although this phenomenon is rare. The incidence of TBE infections in Europe is on the rise with new parts of Europe being added to the list of endemic countries every year, a trend thought to be partly caused by climate change, making further increases in incidence and geographical distribution likely. For this reason any complication related to TBE is of increasing relevance.

CRediT authorship contribution statement

Thomas Agerbo Gaist: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Anna Christine Nilsson:** Data curation, Writing – original draft, Writing – review & editing. **Mette Scheller Nissen:** Writing – original draft, Writing – review & editing. **Matias Adonis Jul Ryding:** Data curation, Writing – review & editing. **Stig Lønberg Nielsen:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Morten Blaabjerg:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Data availability

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

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