CASE REPORT

Tick borne encephalitis without cerebrospinal fluid pleocytosis

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Abstract

Background: Tick borne encephalitis is the most frequent vector-transmitted infectious disease of the central nervous system in Europe and Asia. The disease caused by European subtype of tick borne encephalitis virus has typically a biphasic clinical course with the second phase presenting as meningitis, meningoencephalitis, or meningoencephalomyelitis. Cerebrospinal fluid pleocytosis is considered a condition sine qua non for the diagnosis of neurologic involvement in tick borne encephalitis, which in routine clinical practice is confirmed by demonstration of serum IgM and IgG antibodies to tick borne encephalitis virus.

Case presentation: Here we present a patient from Slovenia, an area highly endemic for tick borne encephalitis, with encephalitis but without cerebrospinal fluid pleocytosis in whom tick borne encephalitis virus infection of the central nervous system was demonstrated.

Conclusion: Cerebrospinal fluid pleocytosis is not mandatory in encephalitis caused by tick borne encephalitis virus. In daily clinical practice, in patients with neurologic symptoms/signs compatible with tick borne encephalitis and the risk of exposure to ticks in a tick borne encephalitis endemic region, the search for central nervous system infection with tick borne encephalitis virus is warranted despite the lack of cerebrospinal fluid pleocytosis.

Background

Tick borne encephalitis (TBE) is the most frequent vector-transmitted infectious disease of the central nervous system (CNS) in Europe and Asia and is considered an emerging disease due to its rising incidence and the spread of endemic areas in recent decades [1]. TBE caused by European subtype of TBE virus (TBEV) has typically a biphasic clinical course with the second phase presenting as meningitis, meningoencephalitis, or meningoencephalomyelitis [2]. Cerebrospinal fluid (CSF) pleocytosis is considered a condition sine qua non for the diagnosis of CNS involvement in TBE, which in routine clinical practice is confirmed by demonstration of serum IgM and IgG antibodies to TBEV [2-4]. Cases of TBE with neurologic involvement but without CSF pleocytosis have been published [5-7], however, only the case recently reported by Pöschl et al. was convincingly substantiated [5]. Here we present a patient from Slovenia, an area highly endemic for TBE [8], with clinical features of encephalitis, who fulfilled criteria for recent CNS infection with TBEV although he had no CSF pleocytosis.

Case presentation

A 79-year-old man with arterial hypertension and chronic venous ulcers on both shins, fell ill acutely with diarrhea, fatigue and sleepiness in midsummer 2013. After a week, diarrhea stopped, but he became febrile up to 38.5°C and was no longer able to walk independently due to general weakness. As a beekeeper he had been exposed to ticks in the past but could not remember having had a tick bite during the preceding few months. At admission to hospital on day 8 of his illness, he was lethargic, disoriented, but without signs of meningeal irritation. His blood pressure was 133/83 mmHg, heart rate 99/min, breathing rate 30/min and axillary temperature 38.9°C. Routine laboratory blood tests revealed normal blood cell count, mild hyponatremia (Na 129; normal 135–145 mmol/l), and slightly elevated concentrations of C-reactive protein (32 mg/l; normal 0–5 mg/l), liver enzymes (aspartate aminotransferase 0.73; normal ≤0.92 μkat/l, gamma-glutamyl transpeptidase 1.12 μkat/l; normal ≤0.92 μkat/l) and creatinine...
(101 μmol/l; normal 44–97 μmol/l). CSF examination yielded elevated protein concentration (1.31 g/l; normal 0.15–0.45 g/l), but normal leukocyte count (3 × 10⁶/l; normal ≤5 × 10⁶/l) and glucose concentration. In the following days the patient remained febrile up to 39.4°C. On day 10, tremor of hands and tongue appeared and his mental status deteriorated to somnolence. Computed tomography of the brain showed only mild periventricular leukopathy. Repeated CSF analyses on day 14 and 23 revealed elevated protein concentrations (1.23, and 2.02 g/l, respectively), but still no pleocytosis (CSF leukocyte count 1, and 2 × 10⁶/l, respectively). PCR analyses of CSF for the presence of TBEV on day 8 and 23 were negative as were for HSV 1, HSV 2, VZV, and enteroviruses. Based on serological results the patient did not have Lyme neuroborreliosis. However, serum IgM and IgG antibodies to TBEV were demonstrated using enzyme linked immunosorbent assay - ELISA (Enzygnost Anti-TBE/FSME Virus IgG, IgM; Siemens, Marburg, Germany) (Table 1). The follow-up levels of specific serum antibodies and the avidity of specific serum IgG (12.7%, 15.4%, and 51.6% on day 14, 21, and 65, respectively) indicated recent infection with TBEV. In addition, demonstration of intrathecal production of anti-TBEV IgM and IgG verified CNS infection with TBEV (Table 1). From day 14 the patient was no longer febrile and his mental and physical status progressively improved. Hospitalization was prolonged because of hospital acquired pneumonia which was treated with amoxicillin/clavulanate. At transfer to a nursing facility on day 32 the patient was afebrile, completely oriented, feeble, but without focal neurological deficit. Routine laboratory test results were unremarkable.

Conclusions
Presenting symptoms and signs of TBE are nonspecific and similar as in acute aseptic meningoencephalitis of other etiologies with fever in 92%, vomiting in 38%, headache in 67-100%, altered consciousness in 12–35.5%, seizures in 0.3-3.3%, tremor in 7-78%, dysphasia in 0.7-3.8%, spinal nerve paralysis in 2.7-15%, and cranial nerve paralysis in 3.3-11% of cases [2,10,15]. Our case, together with the recently published case by Pöschl et al. [5], and some earlier less convincing reports [2,4,10,14]. This finding, however, might be due to a selection bias because in these studies CSF pleocytosis was proven TBE, CSF pleocytosis was established in all cases [2,4,10,14]. This finding, however, might be due to a selection bias because in these studies CSF pleocytosis was one of the inclusion criteria for the diagnosis of TBE [15]. Our case, together with the recently published case by Pöschl et al. [5], and some earlier less convincing reports [6,7], show that CSF pleocytosis is not mandatory in patients with encephalitis caused by TBEV. This is in

| Day | IgM in serum | IgG in serum | IgM in CSF | IgG in CSF | IgM antibody index | IgG antibody index |
|-----|-------------|-------------|------------|------------|--------------------|--------------------|
| 14  | 1.473       | 78.4        | 0.601      | 53.7       | NA                 | NA                 |
| 23  | 1.133       | 130         | 0.676      | 89.7       | 48.6               | 40.2               |

TBEV, tick-borne encephalitis virus; CSF, cerebrospinal fluid; NA, not available.

*Antibody index of intrathecal synthesis of anti-TBEV IgM and IgG calculated according to Reiber's formula [9].
accordance with the reports on encephalitis caused by some other viruses such as herpes simplex 1 in which about 3% of cases take place with normal CSF leukocyte count [16]. The frequency of encephalitis without CSF pleocytosis caused by TBEV infection remains to be determined. However, the paucity of reports implies that such presentation is most probably very rare.

The findings in our patient suggest that in daily clinical practice, in patients with symptoms/signs of encephalitis compatible with TBE and the risk of exposure to ticks in a TBE endemic region, the search for infection with TBEV is warranted despite the lack of CSF pleocytosis. However, to reliably prove that the encephalitis with normal CSF white cell count is caused by TBEV, a proof of TBEV CNS infection is needed besides the usual diagnostic requirements i.e., the evidence of a recent infection with TBEV denoted by the presence of specific serum IgM and IgG antibodies.

Consent
Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
ML, BP, and DS were patient’ clinical doctors. TAŻ carried out the microbiological analyses. DS, FFB., and FS helped to draft the manuscript. All authors read and approved the final manuscript.

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