

doi: 10.48095/ccsnn2021572

Aseptic meningitis during acute hepatitis E – a single center experience

Aseptická meningitida při akutní hepatitidě E – zkušenosti z jednoho centra

Dear Editor,

We would like to describe two rare cases of CNS involvement (aseptic meningitis) in immunocompetent patients with acute hepatitis E, treated at the Department of Infectious Diseases, University Hospital Brno, Czech Republic.

In the last decade, it has been recognized that hepatitis E virus (HEV) is also endemic in the CR with the incidence of about 2.6/100 000 inhabitants [1]. Most cases of hepatitis E in Europe arise from infected animals such as pigs, wild boar, deer and rabbits. Zoonotic HEV genotypes (HEV genotypes 3–8) are mainly food-borne or transmitted by direct contact, but recent data suggest that infection can also be water-borne or iatrogenic through contaminated blood products [2].

Most patients with acute hepatitis E have no symptoms or the symptoms are indistinguishable from other forms of acute viral hepatitis. There have been several extrahepatic manifestations reported with hepatitis E [3–6].

We present two cases of neurological involvement in patients with acute hepatitis E, hospitalized from 2018–2020.

A 45-year-old male, chronically treated for type 2 diabetes and arterial hypertension, was admitted to the hospital 8 days after the onset of headache and subjective slower visual focusing. However, no objective visual disorder or any pathological findings were present in the neurological examination. After normal findings on a brain CT scan and CTA of the brain arteries, a lumbar puncture was performed and meningitis was confirmed (23 lymphocytic cells/ μ L, less than 1 neutrophil/ μ L, 36 erythrocytes/ μ L, total protein 0.334 g/L, 2 oligoclonal bands of the same type found in serum and CSF). Because of elevated liver enzymes upon admission (ALT 5.75, AST 0.9, GGT 7.2 μ kat/L),

viral hepatitis serologies were performed, positive for anti-HEV IgM and IgG antibodies. The test was confirmed by PCR detection of the HEV genotype 3 in the blood, but not in the CSF. Dexamethasone (8 mg t.i.d. for two days then 8 mg b.i.d. for two days and 8 mg on the fifth day) was administered for 5 days as a symptomatic treatment of serous meningitis, and then discontinued, with no other treatment used. All the symptoms disappeared during 8 days of hospital stay and did not recur until one and a half years after the infection.

A 44-year-old female was referred to our department with fever, fatigue, arthralgia, nausea and abdominal pain lasting for 4 days, with significantly elevated serum aminotransferase activity (ALT 38, AST 20.64, GGT 6.87 μ kat/L), and with a slightly elevated serum bilirubin concentration (25.8 μ mol/L). Her medical history included migraine with one attack per month, and she had not traveled abroad for a long time. On the day of admission, she started to complain about a severe headache, which was different than she was used to, while having a migraine attack. She was vomiting and felt unsteady. Physical examination and the ultrasound of the abdomen showed no significant abnormalities. A lumbar puncture was performed, and CSF revealed aseptic meningitis with increased lymphocytic cells count (60/ μ L), normal neutrophils (0.3/ μ L), and a higher level of total protein (1.03 g/L). A serological blood test detected anti-HEV IgM antibodies with anti-HEV IgG antibodies. Following confirmation using the PCR method proved RNA HEV presence in the blood and stool. Oligoclonal bands of the same type were detected in the serum and CSF, while the MRZ reaction was negative. MRI of the brain and cervical spine did not show any pathology. The patient was treated with dexametha-

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Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Accepted for review: 26. 5. 2021

Accepted for print: 4. 11. 2021

some same dosing as above, but 8 mg dose until day seven and mannitol. After corticosteroid administration, the headache was relieved immediately. Regular neurological examination showed normal findings. Liver enzyme serum activity decreased rapidly in the days following admission and corticosteroid administration. After 16 days, the patient was discharged with a serum aminotransferase activity of ALT 1.35 μ kat/L, AST 0.38 μ kat/L, GGT 3.18 μ kat/L and bilirubin concentration 8.4 μ mol/L. HEV was subsequently detected in the CSF also in a very small viral load. The virus sequencing con-

Tab. 1. Basic characteristics of two cases of aseptic meningitis during acute hepatitis E.

Patient / sex	Age (years)	PCR HEV (genotype)	Neurological symptoms	Other symptoms	Bilirubin max (μmol/l)	ALT max (μkat/l)	AST max (μkat/l)	CSF (cells/μl)	Treatment
male	45	blood+ (HEV-3), CSF–	headache, subjective vision impairment	no	11.3	5.75	0.9	23 lymf, < 1 neu, 36 ery	corticosteroids
female	44	blood+, CSF+ (HEV-3c)	headache, vomitus, dizziness	flu-like symptoms, nausea	25.8	38	20.64	60 lymf, 0.3 neu, 0 ery	corticosteroids, mannitol

ALT – alanine transaminase; AST – aspartate transaminase, ery – erythrocytes; GGT – gamma-glutamyl transferase; lymf – lymphocytic cells, neu – neutrophils; PCR – polymerase chain reaction

firmed the HEV-3c genotype. At the follow-up visit a month after discharge, the patient did not mention recurrence of any problems, liver functions were improved, with ALT and AST serum activity in the normal range and GGT slightly elevated (1.30 μkat/L).

Possible extrahepatic manifestations of HEV infection were noted in two patients with acute hepatitis E, as summarized in Tab. 1. These rare cases presented as uncomplicated aseptic meningitis. Both cases were confirmed by HEV RNA detection in the blood or stool. HEV RNA detection in the CSF was positive in one of the two cases. Other causes of infections of the CNS were ruled out by serologic testing (neuroborreliosis, tick-borne encephalitis, herpes simplex virus 1 and 2, varicella and zoster virus, syphilis, hiv human immunodeficiency virus, acute Epstein–Barr virus and cytomegalovirus infection) and serum concentration of C-reactive protein, bilirubin concentration and full blood count within the range of normal values ruled out the possibility of leptospirosis. Both cases were followed up in the consecutive year and no other explanation or ongoing neurological symptoms

have been found. In both cases, corticosteroids were used as part of the treatment (beginning with dexamethasone 8 mg t.i.d. and lowering the dose for 7 days), as there is no evidence-based recommendation for the treatment of CNS complications of acute hepatitis E, and we regularly use such a protocol in the treatment of other viral CNS infections, where there is no causal treatment available. Ribavirin therapy to suppress viral replication does not outweigh the risks of administration, as the HEV infection is self-limited in most cases. Both our cases recovered without sequelae.

Although rare, there are various neurological syndromes during acute hepatitis E infection described in the literature, often seen in patients without signs of hepatitis. Despite the nomenclature of the virus, it is important to emphasize that patients with HEV-associated neurological injury do not usually present with jaundice.

Hepatitis E testing is therefore recommended in cases of neuralgic amyotrophy and Guillain-Barré syndrome, regardless of liver function tests [7]. This appears to be an appropriate next step in the differential dia-

gnosis of serous meningoencephalitis after excluding more common CNS infections.

Funding

This study was funded by the Ministry of Health of the Czech Republic, grant number 17-31921A.

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