Neurologic Disorders and Hepatitis E, France, 2010

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We report meningitis with diffuse neuralgic pain or polyradiculoneuropathy associated with PCR-documented acute hepatitis E in 2 adults. These observations suggest that diagnostic testing for hepatitis E virus should be conducted for patients who have neurologic symptoms and liver cytolysis.

Hepatitis E virus (HEV), a major cause of acute hepatitis in tropical and subtropical countries, is emerging in industrialized countries, where an increasing number of autochthonous hepatitis E cases have been reported (1–5). Nonetheless, the clinical spectrum of HEV infection still might be incompletely characterized. During the past decade, 12 cases of hepatitis E with neurologic signs and symptoms have been reported (1–4, 6–13). We report 2 cases of meningitis or polyradiculoneuropathy in association with PCR-documented acute hepatitis E in France during 2010.

The Cases

Case 1 occurred in a 54-year-old woman hospitalized in August 2010 for subacute diffuse paresthesia and pain of the limbs (with ulnar localization on upper limbs and proximal pain in legs), headaches, cervicalgia, photophobophobia, transient fever, and nausea. Reflexes were all present, without pyramidal signs. No abnormalities were found by medullar magnetic resonance imaging. Nerve conduction study was not done because of rapid clinical improvement beginning <1 week after onset. The patient had no notable medical history. At admission, alanine aminotransferase level was 566 IU/L (reference values 8–34 IU/L), γ-glutamyl transferase level was 184 IU/L (reference 9–38 IU/L), alkaline phosphatase level was 125 IU/L (reference 42–98 IU/L), and bilirubin was 11 μmol/L (reference 5–34 μmol/L). Cerebrospinal fluid (CSF) was clear; protein and glucose levels were 1.03 g/L (reference 0.15–0.45) and 3.4 mmol/L (reference 3.0–4.5 mmol/L), respectively; leukocyte count was 74 cells/mm³, including 90% mononuclear cells; erythrocyte count was 1 cell/mm³. Immunelectrophoresis performed in CSF and serum indicated rupture of the blood–brain barrier. Antibiotherapy with ceftriaxone, amoxicillin, and acyclovir was introduced 2 days after admission and continued for 2 weeks. CSF culture remained sterile at day 5.

Several infectious causes for neurologic symptoms and acute hepatitis were excluded by nucleic acid and serologic assays performed on serum and CSF (online Appendix Table, www.cdc.gov/EID/content/17/8/102028-appT.htm). In contrast, HEV infection was diagnosed by detection of anti-HEV immunoglobulin (Ig) M (cutoff optical density ratio >10; threshold value 1 [Adaltis, Rome, Italy]) and by detection of HEV RNA in serum (5). Concurrently, anti-HEV IgM (Assure, MP Diagnostics, Illkirch, France) and HEV RNA were detected in CSF. HEV RNA levels measured by real-time PCR were ≈2 log greater in the serum (cycle threshold [C] 27) than in CSF (C, 33). HEV RNA open reading frame 2 sequences were recovered from serum (GenBank accession nos. HQ702487 and HQ702490) and CSF (GenBank accession no. HQ702488) by using in-house protocols (14); they showed 100% nt identity with each other. Phylogenetic analysis identified genotype 3, which is commonly found in autochthonous cases in France (4, 5). No source for HEV transmission was identified, including eating undercooked pork or drinking unsafe water; the patient had returned from Greece 3 weeks before her hospitalization. She recovered fully within 2 weeks after onset of hepatitis and neurologic disorders. Liver parameters returned to within normal limits within 2 weeks, and HEV RNA was cleared in serum after 3 weeks.

Case 2 occurred in a 49-year-old man hospitalized in July 2010 for acute proximal sensorimotor weakness of the limbs. Clinical examination showed proximal muscle weakness associated with paresthesia and pain of upper and lower limbs. Muscle stretch reflexes were diminished in the lower limbs. No pyramidal signs were evident. Nerve conduction study results were normal, and needle electromyography showed abnormal spontaneous activity and neurogenic recruitment in weak muscles. The diagnosis of acute inflammatory polyradiculoneuropathy was retained. Liver enzymes were elevated: alanine aminotransferase 78 IU/L (reference <60 IU/L) and γ-glutamyl transferase 81 IU/L (reference <60 IU/L); bilirubin levels were within reference range. CSF was macroscopically clear; protein and glucose levels were

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RNA was detected by real-time PCR only in serum (Ct in serum (optical density ratio >10) but not in CSF. HEV (online Appendix Table). Anti-HEV IgM was detected as in case 1, several infectious etiologies were excluded (online Appendix Table). HEV RNA was detected by real-time PCR only in serum (C, 34). HEV RNA was of genotype 3 (GenBank accession no. HQ702489); nucleotide identity with sequences from case 1 was 91.5%. No source for HEV transmission was identified, and the patient had not traveled abroad. Clinical outcome spontaneously improved within 2 weeks. HEV RNA test results 2 months postadmission were negative.

Conclusions
In these 2 cases, the temporal association between acute hepatitis and neurologic signs and symptoms, atypical neurologic features, and exclusion of a large panel of other potential etiologies are incentive to consider HEV as a possible cause of meningitis, diffuse neuralgic pain, and polyradiculoneuropathy. The association of neurologic signs and symptoms with acute hepatitis E was previously reported for several patients (online Appendix Table). Eight case-patients had Guillain-Barré syndrome (GBS) (3,4,6–11), which has been associated with a variety of bacterial or viral infections, including hepatitis viruses other than HEV (10,11,15). Four other reports described distinct clinical presentations of acute meningoencephalitis with seizure (1), Bell palsy (2), acute transverse myelitis (12), and neuralgic amyotrophy (13).

In most cases, only a few potential etiologies for GBS were tested for. In addition, in all but 2 reported cases (3,4), HEV diagnosis was based only on detection of anti-HEV IgM in serum. Dalton et al. detected HEV genotype 3 RNA in serum from a patient with acute hepatitis E in association with GBS, whereas HEV RNA testing of CSF was negative (3). Kamar et al. described polyradiculoneuropathy with central nervous system involvement in a kidney transplant recipient who had chronic hepatitis E 33 months after acute hepatitis E (4). In this case, HEV RNA was sequenced concurrently in serum and CSF at hospitalization for neurologic involvement. By contrast, the 2 cases in our report occurred concomitantly with acute hepatitis E. In the patient reported by Kamar et al. and in case-patient 1 in this report, HEV RNA load was ≈2 log lower in CSF than in serum (4). Rupture of the blood–brain barrier could have enabled passive entry of the virus into CSF. The negativity of HEV RNA testing in the CSF in case-patient 2 might be explained by lower titers in CSF than in serum because HEV RNA titer in serum was low. In the case reported by Kamar et al., phylogenetic analysis suggested that neurologic symptoms could be associated with emergence of neurotropic variants because clonal HEV RNA in CSF clustered apart from those found in serum. In case-patient 1 reported here, HEV sequences recovered from serum and CSF were 100% identical; nevertheless, they were compared on a short open reading frame 2 fragment (106 nt) and on samples collected at time of acute hepatitis E, whereas comparison was performed 33 months postacute hepatitis in the case reported by Kamar et al. Regarding the outcome of neurologic symptoms associated with acute hepatitis E, patients fully recovered within 1 and 24 weeks, except in the cases reported by Chalupa et al. (10) and Kamar et al. (4). In this latter case-patient, no improvement was noted after 4 months, and the patient died of decompensated cirrhosis.

Previous and current observations suggest that HEV diagnostic testing should be performed for patients who have concurrent neurologic symptoms and liver cytolysis. Further investigations are needed to assess the actual prevalence of HEV infections in cases of neurologic disorders, especially those of unknown etiology.

Addendum

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References

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