CASE REPORT

Acute hepatitis E infection as a cause of unexplained neurological symptoms

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SUMMARY

Neurological disease is the most common extrahepatic manifestation of autochthonous infection with hepatitis E virus (HEV). The association between acute neurological symptoms and hepatitis E is not well known, and hence HEV testing is often omitted. This case describes aberrant neurology in a 35-year-old woman with a background of HEV infection, highlighting the need for increased awareness of acute hepatitis E infection as a cause of unexplained neurological illness.

BACKGROUND

Neurological manifestations of hepatitis E virus (HEV) infection are often overlooked and the opportunity for intervention missed. HEV, a virus with a single-stranded positive-sense RNA genome,¹ is the most common cause of hepatitis.² For many years, hepatitis E was considered an inflammatory pathology of foreign origin. However, autochthonous infection with HEV genotype 3 is becoming increasingly recognised in the West, with a 1 in 2848 prevalence of viraemia among blood donors in the UK.³ Acquisition of the virus is widely reported to result from porcine zoonosis.^{4–7} However, molluscs, crops and other zoonoses remain a possibility.² Whilst ~95% of cases are asymptomatic,⁸ 7.5% of those with clinical manifestation present with neuropathology.⁴ Indeed, aberrant neurology is the most common extrahepatic manifestation of HEV.² HEV has been associated with a range of peripheral neuropathies,^{2,4,9,10} including neuralgic amyotrophy and Guillain-Barré syndrome,^{11,12} as well as cranial nerve palsies and encephalopathies.^{2,5,8,10} Affected individuals are typically younger than those without neurological complication,^{4,13} anicteric and have normal or only mildly atypical liver function.^{8,11} This case illustrates the severity of symptoms that may result from HEV infection and the importance of taking such non-specific symptoms seriously.

CASE PRESENTATION

A 35-year-old woman presented to accident and emergency (A&E) with widespread paraesthesia with associated loss of thermoception. Tactile sensation remained intact, although the patient described a numbness that caused her to perform actions ‘by sight, rather than feel’.

This presentation was on a background of 4 days of symptoms. The illness began nocturnally as an irritative and agonising pain in the legs, manifesting predominantly behind the knees and relieved

on movement. Over the next 48 hours, the pain encroached into the daytime and was triggered by inactivity, such as sitting in the car. While the episodes of pain increased in frequency, the character of the pain remained constant. The pain was accompanied by occasional ‘shivers down the spine’.

Two days after the onset of symptoms, the pain spread to the arm, presenting most notably at the joints.

Seventy-two hours into the illness, the patient became aware of a mental and physical slowing, reporting slowed reaction times and the need for increased concentration when speaking and descending the stairs. She felt emotionally ‘numb’ and experienced a reduced alcohol tolerance, with a distinct worsening of the pain in her limbs after a single glass of wine.

The patient presented to hospital the following day when she could no longer determine the temperature of her shower and the shivers down her spine had become consecutive in nature.

The patient was otherwise medically fit. She had a history of smoking (≤ 2.5 pack years), consumed ~4 units of alcohol per week and enjoyed running and water sports. She was in regular contact with horses, had recently travelled to Europe and described being under stress. The patient’s medical history revealed a head injury and resultant loss of consciousness ~25 years ago, with residual damage to her ‘photographic memory’ and her ability to retain names.

INVESTIGATIONS

On presentation, examination revealed no abnormality. Bloods were taken; a full blood count revealed a slightly reduced platelet count ($129 \times 10^9/L$; 150–400), urea and electrolyte levels were normal, and liver function tests showed a raised alanine aminotransferase (312 U/L; 5–45). Chest X-ray and CT head were unremarkable. The patient was discharged and referred to neurology.

When seen by the neurology consultant 2 days later, there were some clinical anomalies. Reflexes were very brisk, and there was the slightest hint of spasticity in the arms. With a clinical suspicion of encephalomyelitis, an MRI scan was requested. Due to the patient’s encephalopathic, rather than myelopathic, symptoms, the MRI was confined to the brain. The results were normal. Bloods were repeated. Screening for atypical causes of neuropathology indicated a current HEV infection:

Total white cell count (WCC): $3.4 \times 10^9/L$ (4–10).

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Neutrophils: $1.81 \times 10^9/L$ (2–7).
 Platelets: Low normal ($153 \times 10^9/L$).
 Antinuclear antibody screen: Negative.
 Syphilis (IgM, IgG): Negative.
 Vitamin B₉ and B₁₂ (438 ng/L): Normal range.
 Leptospira (Lip 32 DNA, 16S DNA, IgM): Negative.
 Hepatitis E (IgM): Positive, HEV RNA 170 IU/mL.
 Hepatitis E (IgG): Negative.

When repeated 3 weeks later, acute infection had passed, and the patient's symptoms continued to improve, with no persisting pain. The abnormally low WCC and neutrophil count were attributed to the recent HEV infection and were predicted to resolve with time:

Total WCC: $3.6 \times 10^9/L$ (4–10).
 Neutrophils: $1.57 \times 10^9/L$ (2–7).
 Hepatitis E (IgM): Negative, HEV RNA not detected.
 Hepatitis E (IgG): Positive.

DIFFERENTIAL DIAGNOSIS

The patient presented with an evolution of symptoms over the course of 4 days, with central and peripheral features consistent with a diagnosis of encephalomyelitis. The cognitive symptoms and the retention of reflexes implied that, though suggestive, the symptoms were not those of a neuropathy.

Bloods were taken to screen for a number of potential causes of encephalomyelitis, including autoimmune pathology, vitamin deficiencies, Weil's disease and HEV. These investigations revealed a current HEV infection. Other differentials to consider included a neurotropic viral infection and neuroborreliosis. The patient appeared sufficiently well that, with no clinical signs of meningeal irritation, it was felt that a lumbar puncture was not necessary. Borreliosis screening was not included in the first instance due to the infection's self-limiting course and because, while arthralgia and neurological complications are consistent with the later clinical presentation of Lyme disease, the absence of erythema migrans and other suggestive clinical features resulted in a low level of clinical suspicion.

TREATMENT

HEV is ordinarily a self-limiting infection in immunocompetent individuals,¹³ including cases of HEV-associated meningoencephalomyelitis.² On presentation at the neurology clinic, the patient reported symptomatic improvement, and a decision was made to monitor the patient at follow-up appointments.

OUTCOME AND FOLLOW-UP

At the 6-month follow-up, the patient was asymptomatic, with full resolution of symptoms reported from 1 month postinfection. Liver function tests, WCCs and neutrophils were normal. This presentation matches that of a typical HEV-associated monophasic neurological disorder, described in the literature as progressing quickly and resolving over a longer period of time.¹³

DISCUSSION

It has been predicted that 100 000 people are infected with HEV genotype 3 every year in the UK.³ While only 5% are symptomatic,⁸ neurological presentation in 7.5% of this cohort indicates that HEV may be responsible for 375 cases of acute neurological illness annually.⁴ The observation that only ~100 cases of HEV-related neurological illness were reported between 2011 and 2017,² predominantly within Europe and Asia, highlights the potential scale of undetected or unreported cases. From another perspective, HEV has been associated with 2.4% of

non-traumatic neurological presentations,⁸ including 10.6% of neuralgic amyotrophy cases and 5% of Guillain-Barré syndrome cases.^{12–14} Hence, it is worthy of consideration in cases of abnormal neurology.

The exact mechanism by which HEV leads to neurological involvement remains unknown. It has been argued that neural damage is immune mediated (supported by reports of delays between infection and neuropathological presentation),¹⁴ that it may result from HEV-evoked autoimmunity (substantiated by links between HEV and autoimmune thyroiditis),^{15–16} and that HEV can act as a neurotropic agent, directly affecting the central nervous system. The latter is supported by evidence that HEV genotype 4 can cross the blood–brain barrier,¹⁷ and the discovery of different HEV quasispecies in the serum and cerebrospinal fluid of a kidney transplant patient.¹⁸ Regardless of the pathophysiology, a clear temporal link is demonstrated between HEV infection and neurological disease in case reports, such as this one, throughout the literature.

While the patient in this case report experienced a full resolution of symptoms without treatment, it is important to note that not all patients are so fortunate. One study showed that 62.5% of those with HEV-associated neuropathology were still experiencing residual neurological symptoms 5 years after initial

Patient's perspective

At the time of onset of these symptoms I was severely run down with stress and fatigue. I had recently completed a 190 km non-stop bike race in Norway and work at that time was extremely stressful. So, when the symptoms occurred, I actually thought I was just fatigued.

I first felt a pain at the back of my knees and to relieve the pain I had to straighten and bend my knees repeatedly in quick movements. The knee pain would happen when I was still, for example, while driving or sitting. It then happened at night too and I'd lie in bed rapidly bending and straightening my knees. Episodes would take anything from 2 min to the whole night. 2 days after initial onset, the same thing then started to happen in my arms, with less intensity and mostly at night. Again, I'd have to bend and straighten my elbows to relieve the pain.

My coordination was slow and it felt like I couldn't lift heavy things, although I could if I just concentrated. If someone would throw a ball at me, I'd know it was coming, but I would not be able to react to catch it or stop it from hitting me. I felt floppy all over, as if my muscles were like jelly.

Walking down stairs was a challenge. I knew I could to it, but I really had to concentrate and almost tell my legs what to do.

The final symptom which led me to A&E was that when I got in the shower, I couldn't feel the temperature of the water.

From initial onset to the time of going to A&E was roughly 4 days.

After my trip to A&E, the symptoms started to wane and over the course of the next week the pain stopped in my knees and elbow and my coordination got better. I did feel fatigued and run down for weeks, perhaps months, after this, but that could have also been due to other factors.

Now I feel completely recovered and so relieved by the diagnosis, as when I had those neurological symptoms I did think the worst—that I had some terminal disease.

I'd also like to say that the NHS was absolutely amazing, from the staff at A&E to the doctor who diagnosed me. I am so thankful for the care and attention that I received.

symptom onset.⁴ There is also evidence that, while the role of HEV in neurological disease aetiology might not always alter clinical outcome, it can worsen the severity of neurological symptoms. This has been reported in HEV-associated neuralgic amyotrophy and Guillain-Barré syndrome.^{11 12 14} Hence, a diagnosis of HEV when the patient is viraemic (using PCR or IgM screening) and the subsequent implementation of antiviral intervention may reduce the incidence of chronic neuropathology and lessen the severity of symptoms. Ribavirin monotherapy has been described as an effective treatment for acute HEV infection and may prove useful in this role.⁶

The relatively recent appreciation of HEV-associated neuropathology, first reported in 2000,¹⁹ means that understanding of this phenomenon is still in its infancy. It will be important to perform and report HEV screening results routinely to obtain an accurate idea of the scale of HEV's contribution to atypical neurological disease. While MRI and CT scans appeared normal in this case, the sensitivity of such imaging to HEV-related lesions also remains unclear. Hence, more research in this field is required. Better awareness of hepatitis E-associated neurological illness and a higher level of suspicion, with closer scrutiny of symptoms, signs and liver function tests, is necessary if we are to quantify, understand and learn to treat such illness.

Learning points

- Infection with hepatitis E virus (HEV) genotype 3 is common in the UK.
- Consider current or recent HEV infection in cases of radiculoplexoneuropathy and encephalomyelitis in the presence of normal or mildly atypical liver function tests.
- Increased awareness and recognition of HEV-associated neurological disease will help to quantify, understand and learn to treat such illness.

Contributors This interesting case was brought to LB's attention by a consultant at the teaching hospital in which LB was placed. LB took a detailed history from the patient and originally drafted the report. PM then assisted in revising the report, providing insight into the patient's clinical manifestation, differentials and investigations.

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