CASE REPORT

Transverse myelitis caused by hepatitis E: previously undescribed in adults

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SUMMARY

We report the case of a 62-year-old Caucasian woman who was admitted with urinary retention and lower limb paraesthesia following a week's prodromal illness of headache and malaise. Liver function tests showed a picture of acute hepatocellular dysfunction. She developed reduced lower limb power, brisk reflexes, extensor plantars, a sensory level at T8 and reduced anal sphincter tone, establishing a clinical diagnosis of transverse myelitis. A spinal MRI showed no evidence of cauda equina or spinal cord compression. Cerebrospinal fluid (CSF) analysis showed raised protein and raised white cell count. Hepatitis E IgM and IgG were positive and hepatitis E virus was found in her CSF. She was treated with methylprednisolone and is slowly recovering with physiotherapy.

BACKGROUND

To the best of authors' knowledge, hepatitis E in association with acute transverse myelitis has never previously been described in an adult. The one case from the literature is a 12-year-old child in India. Hepatitis E-associated Guillain-Barré syndrome has become an established entity and is regularly tested for. We hypothesise that our link to transverse myelitis is more common than previously recognised. We believe that all patients with an inflammatory cord syndrome and deranged liver function tests (LFTs) should be tested for hepatitis E.

CASE PRESENTATION

Referral and presenting symptom

Our 62-year-old patient was admitted to the acute medical ward with a 7-day history of malaise and headache. She had experienced 2 days of lower back pain, paraesthesia in her feet and heaviness in her legs. She was experiencing difficulty passing urine. She had no bowel disturbance.

Medical history

Hysterectomy (uterine fibroids); viral illness 3 months previously.

Medication

No regular medications.

Social and family history

The patient lived with her husband in a rural location surrounded by woodland, and had regular contact with horses. She was a lifelong non-smoker with no pets. She had spent a week on holiday in Turkey 2.5 months prior to presentation. She drank 30 units of alcohol a week.

Examination

Vital signs on admission were: temperature 36.2°C, pulse rate 92 bpm (regular), blood pressure 193/137 mm Hg and respiratory rate 16 breaths/minute. The patient was alert and had a Glasgow Coma Scale Score of 15/15.

Examination of neurological system revealed power 5/5 throughout, normal tone, reflexes symmetrical and normal, plantars down-going, sensation normal. She had normal anal tone and normal perianal sensation. Cardiovascular, respiratory and gastrointestinal systems examination was unremarkable.

Within 24 h, there was a change in the neurological examination. Power was found to be 4/5 symmetrically in her lower limbs, with normal tone and reflexes. She had reduced anal sphincter tone. Her power deteriorated and eventually she had power of 0/5 in her lower limbs. Her reflexes were brisk and her plantars became extensor. She developed sensory loss to all modalities up to a level of T8.

INVESTIGATIONS

Blood tests on admission showed deranged LFTs. Alanine transaminase (ALT) was raised at 1152 units/L, alkaline phosphatase (ALP) was 196 units/L, bilirubin was 6 units/L and albumin 37 units/L. Renal function and electrolytes were normal, as were the full blood count, coagulation screen and calcium. The C reactive protein was 16 mg/dL. HIV test was negative, as was mycoplasma serology. Lyme serology was negative.

Nerve conduction studies showed no evidence of peripheral nerve dysfunction. Ultrasound of the abdomen was unremarkable. MRI of the spine showed no evidence of cauda equina syndrome, and no spinal cord compression. ECG revealed sinus rhythm.

At Public Health England, Birmingham Heartlands Hospital, the patient's hepatitis E virus (HEV) IgM and IgG antibodies were found to be positive, using an ELISA kit from Mikrogen Diagnostik, Germany. This gave a qualitative result with an optical density value over the cut-off point, confirming a positive result. This was reconfirmed using a Fortress diagnostics ELISA assay, at the Virus Reference Department, Public Health England, Colindale, London. Viral load was obtained using an in-house Taqman PCR assay (amplifying across part of the ORF 2 region, which encodes for the capsid protein). On admission, HEV IgM was reactive (signal to cut-off ratio, ie, S/CO—9.893 with an IgG level of 12.663).

Plasma HEV RNA level was 9700 IU/mL. On analysis of genotyping, this patient had been infected with hepatitis E genotype 3 (HEV3).

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Genotype 3 viruses can infect human beings as well as pigs (and other mammalian species).¹ HEV3 have been detected in patients with acute hepatitis E, suggesting that HEV-positive meat might be the source of infection (porcine zoonosis).¹ The virus strain in our patient was very similar to viruses circulating in the UK.

An additional blood sample was sent prior to discharge (7 weeks after the initial sample was sent). The patient's HEV IgM remained positive (although reactivity had dropped to a S/CO of 2.363) and IgG levels had risen to a S/CO of 19.9. Her plasma sample showed that HEV RNA was undetectable at this point. Isolation of HEV from faecal matter was not attempted, although this would have given an interesting insight.

Cerebrospinal fluid (CSF) examination showed raised white cell count (79 cells/ μ L with 95% polymononuclear cells), and raised protein: 0.72 g/L. CSF glucose was 3 mmol/L (serum: 4.6 mmol/L), with the presence of oligoclonal bands identical in serum and CSF. HEV RNA was performed on the CSF, at Colindale, using the in house Taqman endogenous control assay. The patient had a low viral load (30 IU/mL), with the limit of detection of this assay at 22 IU/mL. Although the CSF result is an interesting observation in context of the patient's symptoms, the blood serology unequivocally demonstrated HEV infection. There is little chance of blood having contaminated the CSF as that sample contained only 4 red blood cells/ μ L.

DIFFERENTIAL DIAGNOSIS

The differentials included infectious/parainfectious myelitis.

TREATMENT

Aciclovir and ceftriaxone were started. The neurological symptoms progressed despite the antiviral/antibiotic. The patient was given two courses of pulsed methylprednisolone and started on oral prednisolone. Unfortunately, her neurology did not directly respond to any of these treatments. Her case was discussed with the local hepatology team, which did not feel that we should give any further-specific treatment targeted at hepatitis E. Her LFTs had improved during her stay and, prior to discharge, her ALT was 147 units/L, ALP was 101 units/L and bilirubin was 5 units/L.

OUTCOME AND FOLLOW-UP

The patient was transferred to a spinal rehabilitation unit and subsequently discharged home as she was improving well with physiotherapy.

DISCUSSION

Hepatitis E was formerly considered a travel-associated, self-limiting disease. It can be contracted through contaminated water or food. In England and Wales, a total of 869 cases of hepatitis E were reported in 2014 compared with a total of 692 cases last year. This is consistent with the on-going increase in cases observed since 2010.²

There are four major genotypes, representing a single serotype. It is a single-stranded, non-enveloped RNA virus. In developed countries, HEV occurs mostly in middle-aged and elderly men, with an associated mortality of 5–10%.³ We do not know if there is a correlation between HEV viral load or genotype and the extent of neurological syndrome. We cannot estimate the rate of transverse myelitis caused by HEV, as often the nature of HEV infection is either subclinical or self-terminating.

Testing for hepatitis E is now recommended as part of the diagnostic analysis of all patients with acute or chronic hepatitis.⁴ It is diagnosed in immunocompetent individuals based on the detection of anti-HEV IgM and anti-IgG, and also through

the detection of HEV RNA. Clonal HEV sequences in the serum and CSF showed quasispecies compartmentalisation, suggesting that neurological symptoms could be linked to the emergence of neurotropic variants.⁵

Extrahepatic manifestations of hepatitis E include renal complications,⁶ acute pancreatitis⁷ and thrombocytopaenia.⁸ It is well understood that hepatitis E can cause neurological complications as well, including Guillain-Barré syndrome, meningoencephalitis and brachial neuritis.^{9–14}

The temporal association between acute hepatitis and neurological signs and symptoms, with exclusion of a large panel of other possible aetiologies, leads us to the conclusion that our patient is the first adult patient described in the literature to have an acute hepatitis E infection leading to a cord syndrome. Transverse myelitis has been described in association with hepatitis A, B and C.^{15–18} The proposed aetiologies include direct viral invasion and an autoimmune-mediated myelitis. Direct viral invasion would be implicated when the virus is isolated from the CSF of the affected patient.

There is one case study published in Indian Paediatrics, which describes a 12-year-old girl who presented with a cord syndrome following a prodromal illness of fever, anorexia and jaundice, later attributed to hepatitis E with positive IgM for HEV. She spontaneously recovered without needing immunotherapy.¹⁹

Treatment of hepatitis E is not normally needed in an immunocompetent patient, as the disease usually resolves spontaneously. Treatments that have been used to treat patients with immunocompromise are pegylated interferon α and ribavirin. These have been used in several cases to good effect. In addition, any iatrogenic immunosuppression can be reduced.²⁰ There is little evidence that sheds light on whether antiviral treatment should be offered to patients with hepatitis E-associated neurological disorders (in addition to the standard treatment options of intravenous immunoglobulin, plasma exchange and steroids).

An important area of future research is whether it would improve outcomes if acute hepatitis E-associated transverse myelitis is treated with antiviral agents, in addition to the immunotherapies commonly used for this condition.

Learning points

- Serological testing for hepatitis E should be considered for a presentation with deranged liver function tests and acute neurological symptoms.
- In cases of transverse myelitis of uncertain aetiology, hepatitis E testing should be considered, including looking for presence of the virus in the cerebrospinal fluid.
- Treatment options for this rare complication of hepatitis E could be explored to optimise prognosis.

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Competing interests None declared.

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REFERENCES

- 1 Kamar N, Bendall R, Legrand-Abravanel F, *et al.* Hepatitis E. *Lancet* 2012;379:2477–88.
- 2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404107/hpr0515_zoos.pdf Health Protection Report Vol. 9 No. 5–13 February 2015 (accessed 10 Mar 2015).
- 3 Dalton H, Bendall R, Ijaz S, *et al.* Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* 2008;8:698–709.
- 4 Ijaz S, Said B, Gajraj R, *et al.* Public health operational guidelines for hepatitis E Health protection response to reports of hepatitis E infection. Published January 2015, Page: 9. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/396909/PH_Operational_Guidelines_for_HepE_051214_Standard_template_CT.pdf
- 5 Kamar N, Izopet J, Cintas P, *et al.* Hepatitis E virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. *Am J Transplant* 2010;10:1321–4.
- 6 Ali G, Kumar M, Bali SK, *et al.* Hepatitis E associated immune thrombocytopenia and membranous glomerulonephritis. *Indian J Nephrol* 2001;11:70–2.
- 7 Deniel C, Coton T, Brardjanian S, *et al.* Acute pancreatitis: a rare complication of acute hepatitis E. *J Clin Virol* 2011;51:202–4.
- 8 Fourquet E, Mansuy JM, Bureau C, *et al.* Severe thrombocytopenia associated with acute autochthonous hepatitis E. *J Clin Virol* 2011;48:73–4.
- 9 Kejariwal D, Roy S, Sarkar N. Seizure associated with acute hepatitis E. *Neurology* 2001;57:1935.
- 10 Rianthavorn P, Thongmee C, Limpaphayom N, *et al.* The entire genome sequence of hepatitis E virus genotype 3 isolated from a patient with neuralgic amyotrophy. *Scand J Infect Dis* 2010;42:395–400.
- 11 Fong F, Illahi M. Neuralgic amyotrophy associated with hepatitis E virus. *Clin Neurol Neurosurg* 2009;111:193–5.
- 12 Loly JP, Rikir E, Seivert M, *et al.* Guillain-Barré syndrome following hepatitis E. *World J Gastroenterol* 2009;15:1645–7.
- 13 Sood A, Midha V, Sood N. Guillain-Barré syndrome with acute hepatitis E. *Am J Gastroenterol* 2000;95:3667–8.
- 14 Kamani P, Baijal R, Amarapurkar D, *et al.* Guillain-Barre syndrome associated with acute hepatitis E. *Indian J Gastroenterol* 2004;24:216.
- 15 Aktipi KM, Ravaglia S, Ceroni M, *et al.* Severe recurrent myelitis in patients with hepatitis C virus infection. *Neurology* 2007;68:468–9.
- 16 Trevisani F, Gattinara GC, Caraceni P, *et al.* Transverse myelitis following hepatitis B vaccination. *J Hepatol* 1993;19:317–18.
- 17 Tyler KL, Gross RA, Cascino GD. Unusual viral causes of transverse myelitis: hepatitis A virus and cytomegalovirus. *Neurology* 1986;36:855–8.
- 18 Stübgen JP. Immune-mediated myelitis associated with hepatitis virus infections. *J Neuroimmunol* 2011;239:21–7.
- 19 Mandal K, Chopra N. Acute transverse myelitis following hepatitis E virus infection. *Indian Pediatr* 2006;43:365–6.
- 20 Gerolami R, Borentain P, Raissouni F, *et al.* Treatment of severe acute hepatitis E by ribavirin. *J Clin Virol* 2011;52:60–2.

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