CASE REPORT

Older men with unexplained hepatitis

Kok Haw Jonathan Lim,¹ Mark Howard,² Neil Jackson,¹ Sumita Verma^{1,3}

¹Department of Gastroenterology & Hepatology, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK
²Department of Pathology, Brighton and Sussex University Hospitals, Brighton, Sussex, UK
³Brighton and Sussex Medical School, Brighton, UK

Correspondence to

Dr Kok Haw Jonathan Lim,
 jonathan.lim@doctors.org.uk

Accepted 20 May 2014

SUMMARY

A 59-year-old Caucasian man presented with painless jaundice for 6 weeks. He drank 70 units of alcohol per week. Examination revealed jaundice, spider angiomas and a 3 cm firm hepatomegaly. Initial bloods: bilirubin 152 $\mu\text{mol/L}$, alanine aminotransferase 1484 IU/L, alkaline phosphatase 130 IU/L, γ -glutamyl-transpeptidase 1224 IU/L and International Normalised Ratio 1.1. A standard liver screen was normal, and an abdominal ultrasound/CT scan suggested cirrhosis, confirmed by liver biopsy on day 5. Hepatitis E virus (HEV) serology on day 6 indicated acute infection. He developed severe hepatic decompensation characterised by worsening jaundice, ascites and variceal bleeding. On day 33 ribavirin 600 mg was initiated though discontinued after 2 weeks on receipt of a negative HEV RNA. At the last follow-up he had recovered, and remains abstinent from alcohol. We describe a case of autochthonously (locally) acquired HEV infection with life-threatening hepatic decompensation in the presence of undiagnosed alcohol-related cirrhosis.

BACKGROUND

In the western world hepatitis E virus (HEV) infection is considered a zoonotic disease. Middle-aged to elderly men are particularly susceptible, especially in the presence of immunosuppressive states such as alcohol excess and chronic liver disease (CLD). We describe the case of a patient with acute hepatitis E who developed life-threatening hepatic decompensation in the presence of undiagnosed cirrhosis. A timely diagnosis is paramount to prevent unnecessary investigations as well as to enable the potential use of antiviral therapy.

CASE PRESENTATION

A 59-year-old Caucasian homosexual man presented in June 2012 with painless jaundice for 6 weeks. He drank 70 units of alcohol per week and admitted to having unprotected sexual activity 7 weeks ago. There was no history of liver disease, or recent travel. Examination revealed presence of jaundice, a few spider angiomas and a 3 cm firm hepatomegaly.

INVESTIGATIONS

Initial bloods: bilirubin 152 $\mu\text{mol/L}$, alanine aminotransferase 1484 IU/L, aspartate aminotransferase 1121 IU/L, alkaline phosphatase 130 IU/L, γ -glutamyl-transpeptidase 1224 IU/L and International Normalised Ratio (INR) 1.1. A standard liver screen (excluding HEV serology) was normal, and an abdominal ultrasound and CT scan suggested cirrhosis (nodular liver and splenomegaly). A percutaneous liver biopsy performed on day 5 confirmed

cirrhosis with portal and lobular inflammation consistent with superimposed acute hepatitis (figure 1).

OUTCOME AND FOLLOW-UP

HEV serology was eventually requested on day 6 being consistent with an acute infection (HEV IgG, IgM and RNA positive, HEV genotype not performed due to low HEV RNA titre). Serum bilirubin increased to 500 $\mu\text{mol/L}$ and ursodeoxycholic acid was initiated. Liver transplant was not an option due to the recent alcohol history and he was discussed with the regional centre.

He was discharged on day 11 (stable bilirubin ~ 500 , INR 1.2) with aim for weekly bloods in primary care. On subsequent review in the clinic on day 37 bilirubin and INR had increased to 630 $\mu\text{mol/L}$ and 1.4, respectively. Repeat HEV RNA was requested and initiated with ribavirin 600 mg once daily. Unfortunately, he was readmitted 4 days later with nausea and weakness, and then had two further admissions with ascites and variceal bleeding (treated with endoscopic banding and propranolol).

Ribavirin was discontinued 2 weeks later on receipt of a negative HEV RNA, though by this time his serum bilirubin showed a downward trend (figure 2). At the last clinical follow-up in November 2012 he had recovered with resolution of jaundice (figure 2) and ascites, and remains abstinent from alcohol.

DISCUSSION

We describe the case of a patient with autochthonously (locally) acquired HEV infection who had life-threatening hepatic decompensation in the presence of undiagnosed cirrhosis. Although the case had the risk profile for autochthonous HEV

Figure 1 H&E stain $\times 200$ magnification showing fibrotic bands (cirrhosis; thick arrow), feathery degeneration of hepatocytes and persisting lobular and portal inflammation.

CrossMark

To cite: Lim KHJ, Howard M, Jackson N, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202561

Figure 2 Trend of liver tests over time.

infection (older man with underlying immunosuppressive condition),^{1–3} there was delay in requesting HEV serology, most likely due to lack of travel history.

HEV, an RNA virus belonging to the Hepeviridae family⁴ is considered to be the most common cause of acute viral hepatitis worldwide.⁵ Acute HEV is diagnosed in the presence of a positive HEV serology (IgM and IgG) with or without a positive HEV RNA, though an HEV RNA is mandatory in immunosuppressed patients.⁶ Liver biopsy is not necessary to make a diagnosis.⁶

Disease epidemiology is very different in the developing and western world. In the former, HEV (genotypes 1 and 2) is acquired via the faeco-oral route, affects young individuals, resulting in a self-limiting icteric illness, except in pregnant women where mortality can be high (~25%).⁷ In contrast, in the western world autochthonously acquired HEV infection (genotype 3) is considered a zoonotic disease, transmitted by eating undercooked meat (pork, deer and boar).^{8,9} However, the source and route of infection cannot be identified in most including our case.¹⁰ It is often asymptomatic but can also result in an acute hepatitis.¹⁰ It affects older men (median age ~65 years) especially those with alcohol excess, CLD and solid organ transplants.^{1–3} In the former HEV superinfection can result in life-threatening hepatic decompensation² and in the later the infection can become chronic with the development of cirrhosis.³

Hepatitis E infection is rarely considered a diagnostic possibility as a cause of hepatic decompensation in patients with CLD in developed countries.¹⁰ In contrast, in developing countries HEV may account for 60% of all decompensation with high 3-month mortality (44.6%).¹¹ Despite the low HEV RNA, hepatitis E infection was the most likely aetiology for the hepatic decompensation in this case. HEV viraemia is transient¹⁰ and the virus is not directly cytopathic (liver injury occurring due to host-mediated immune responses),¹² thus there is no correlation between HEV RNA levels and severity of liver disease.¹³ A systematic study is currently underway looking for the presence of HEV in patients with decompensated liver disease in the UK.¹⁴

In England, HEV seroprevalence rates are 13% increasing to 25% in those >50 years, with an annual attack rate of 0.1%, equating to 62 000 infections/year.¹⁵ These data suggest that most cases of HEV infection in the UK are subclinical or undiagnosed^{10,15} and probably also in the USA where there are no Food and Drug Administration-approved serological tests.¹⁰ In fact a high proportion of clinicians do not test for HEV

unless the patient reports a recent history of travel to a disease endemic area.¹⁶ A retrospective analysis showed that 21% of patients diagnosed with drug-induced liver injury actually had autochthonous hepatitis E.¹⁷

There is preliminary data to suggest that HEV is sensitive to ribavirin (an antiviral agent) which has been successfully used to treat severe hepatitis E infection in European patients with underlying CLD.¹⁸ In our case, cholestasis improved on initiation of ribavirin, though this may have been coincidental as he was subsequently found to be HEV RNA negative at the time of ribavirin initiation. Nonetheless, our case report will increase awareness about the prompt consideration for antiviral therapy in the setting of severe HEV infection. An HEV vaccine has recently been licensed for use in China (HEV-239)¹⁹ but remains to be tested in patients with CLD.

Learning points

- ▶ Middle-aged to elderly men are particularly susceptible to hepatitis E virus infection, especially in the presence of immunosuppressive states such as alcohol excess and chronic liver disease.
- ▶ Irrespective of a travel history, hepatitis E serology should be requested in any patient with unexplained hepatitis.
- ▶ A timely diagnosis is paramount to prevent unnecessary investigations as well as enable the potential use of antiviral therapy.
- ▶ Those with severe or chronic infection could be considered for antiviral therapy.

Acknowledgements All the authors are grateful to Dr Harry Dalton, Consultant Gastroenterologist and Hepatologist, Royal Cornwall Hospital Trust for his excellent critique of the manuscript.

Contributors KHJL was responsible for data collection and for writing the first draft; MH provided histological data; NJ provided clinical care; SV contributed to the intellectual content and critical revisions. All authors were involved in the revisions of the manuscript and approved the final draft. SV is the guarantor.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Said B, Ijaz S, Kafatos G, *et al.* Hepatitis E Incident Investigation Team. Hepatitis E outbreak on cruise ship. *Emerg Infect Dis* 2009;15:1738–44.
- 2 Péron JM, Bureau C, Poirson H, *et al.* Fulminant liver failure from acute autochthonous hepatitis E in France: description of seven patients with acute hepatitis E and encephalopathy. *J Viral Hepat* 2007;14:298–303.
- 3 Kamar N, Abravanel F, Selves J, *et al.* Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. *Transplantation* 2010;89:353–60.
- 4 Emerson SU, Nguyen H, Graff J, *et al.* In vitro replication of hepatitis E virus (HEV) genomes and of an HEV replicon expressing green fluorescent protein. *J Virol* 2004;78:4838–46.
- 5 Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol* 2008;48:494–503.
- 6 Kamar N, Bendall R, Legrand-Abravanel F, *et al.* Hepatitis E. *Lancet* 2012;379:2477–88.
- 7 Rein DB, Stevens GA, Theaker J, *et al.* The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology* 2012;55:988–97.
- 8 Teshale EH, Hu DJ, Holmberg SD. The two faces of hepatitis E virus. *Clin Infect Dis* 2010;51:328–34.
- 9 Mizuo H, Yazaki Y, Sugawara K, *et al.* Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido, Japan. *J Med Virol* 2005;76:341–9.

- 10 Scobie L, Dalton HR. Hepatitis E: source and route of infection, clinical manifestations and new developments. *J Viral Hepat* 2013; 20:1–11.
- 11 Radha Krishna Y, Saraswat VA, Das K, *et al.* Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. *Liver Int* 2009;29:392–8.
- 12 Agarwal R, Jameel S. Hepatitis E. *Hepatology* 2011;54:2218–26.
- 13 Legrand-Abravanel F, Kamar N, Sandres-Saune K, *et al.* Characteristics of autochthonous hepatitis E virus infection in solid-organ transplant recipients in France. *J Infect Dis* 2010;202:835–44.
- 14 Dalton HR, Bendall R, Ijaz S, *et al.* Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* 2008;8:698–709.
- 15 Ijaz S, Vyse AJ, Morgan D, *et al.* Indigenous hepatitis E virus infection in England: more common than it seems. *J Clin Virol* 2009;44:272–6.
- 16 Lewis HC, Boisson S, Ijaz S, *et al.* Hepatitis E in England and Wales. *Emerg Infect Dis* 2008;14:165–7.
- 17 Dalton HR, Fellows HJ, Stableforth W, *et al.* The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther* 2007;26:1429–35.
- 18 Péron JM, Dalton H, Izopet J, *et al.* Acute autochthonous hepatitis E in western patients with underlying chronic liver disease: a role for ribavirin? *J Hepatol* 2011;54:1323–4; author reply 1234–5.
- 19 Zhu FC, Zhang J, Zhang XF, *et al.* Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010;376:895–902.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow