A rare but important cause of fulminant hepatic failure

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DECLARATIONS

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The incidence of hepatitis E in the UK is increasing. We recommend measuring hepatitis E serology in those with an acute hepatitis.

Case report

A 79 year-old Caucasian man presented to our institution with jaundice and dark urine having fallen from a ladder in his stables three days prior to admission. The fall had left him with some discomfort for which he had self-medicated with paracetamol. He denied having exceeded the recommended dose of paracetamol. There was no past medical history of liver disease, illicit drug use, drugs known to cause liver failure, or any history of foreign travel. Physical examination revealed icterus in the absence of clinical stigmata of chronic liver disease.

Haematological and biochemical parameters were consistent with acute hepatitis. The synthetic function of the liver showed a rapidly worsening trend with an initial albumin of 33 g/L that worsened to 18 g/L and an initial INR of 1.4 that deteriorated to 2.5. Serology was negative for hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus and cytomegalovirus. HIV status was not tested. Autoantibodies, alpha 1 antitrypsin, immunoglobins, ferritin and copper were in the normal range. Serum paracetamol was undetectable. An electrocardiogram did not show any ischaemic features. An abdominal computed tomography scan did not demonstrate any abnormality in the liver, with a patent hepatic vein and no radiological evidence of portal hypertension or cirrhosis.

Initially, the working diagnosis was paracetamol induced subfulminant liver failure as a result of therapeutic misadventure. Intravenous N-acetyl cysteine therapy was commenced. Despite these and general supportive measures the patient continued to deteriorate with worsening liver function tests. Subsequently he became encephalopathic and developed renal failure and pneumonia and was considered too unstable for consideration of an orthotopic liver transplant. He failed to respond to further treatment and died two weeks after presentation. Hepatitis E virus (HEV) serology taken ante-mortem was positive for anti-HEV IgM and anti-HEV IgG thus suggesting a diagnosis of acute HEV infection. A postmortem liver biopsy demonstrated histological changes consistent with an acute hepatitis with submassive necrosis.

Discussion

HEV is a small non-enveloped single stranded RNA virus that causes an acute hepatitis similar to hepatitis A.[1] The HEV has a single serotype, with four genotypes having been identified. HEV genotypes 1 and 2 exclusively infect humans, whereas genotypes 3 and 4 infect human and other animals, most notably swine. Transmission is predominantly through the faecal-oral route, most often through contamination of water supplies and food and less commonly vertically or parenterally. Thus, HEV is particularly prevalent in developing countries where basic sanitation is poor. In such areas, mortality from acute HEV is 0.5–3%, increasing to 20% in pregnancy.[1] HEV is considered rare in the UK and predominately occurs in travellers returning from endemic areas. Mortality from acute HEV in the UK is significant at around 4%.[2] A recent

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study from Italy examined 651 patients with acute (non-A–C) hepatitis, and found that 20.6% patients tested had acute HEV thus suggesting it is not uncommon.[3]

In the UK, 311 cases of acute HEV were reported between 1993–2002 yet between 2003–2008 a further 632 cases were reported.[2] These data suggest a possible increase in the incidence of HEV in the UK. However, this may only be a pseudo-increase reflecting increasing awareness of HEV among healthcare professionals.[4] The increase in incidence of HEV is supported by recent publications identifying cases in Birmingham,[5] Hereford,[2] and Devon and Cornwall.[6] It is postulated that many of these cases were found to have acquired HEV from the UK.

It has been proposed that the increase in prevalence in the UK is secondary to the consumption of contaminated boar, pig, deer and venison meat. In the UK, there have been reports of HEV being associated with the consumption of uncooked pork and shellfish.[7] Studies have demonstrated that 85% of UK pigs are anti-HEV positive.[8,9] However, data are conflicting with a recent study suggested that exposure to pigs was not a significant risk factor for acquiring HEV.[10]

It is interesting to note that the patient presented herein lived in a rural setting in Staffordshire. Although his water was supplied from the mains, he did spend a considerable time pursuing countryside activities. We hypothesize that these may be the source of HEV acquisition. Of note is that this case significantly differs from previous reports of UK acquired acute HEV infection in that they were associated with a self-limiting illness rather than acute fulminant liver failure associated with mortality.

Drug-induced liver injury is relatively common in the UK, accounting for 50% of all cases of acute liver failure. A recent UK study has examined the rates of HEV infection in subjects diagnosed with drug-induced liver injury as it also presents with a clinical picture similar to that of acute HEV infection. Of 47 patients with a diagnosis of drug-induced liver injury, six had serology positive for HEV.[11] This study concludes that in those patients in whom drug-induced liver injury is suspected, HEV serology should be concomitantly tested with other standard serology parameters.

HEV is usually a self-limiting illness and the focus of management is excluding other causes of acute hepatitis in association with supportive treatment. Orthotopic liver transplantation for acute fulminant liver failure secondary to HEV has not, to the best of our knowledge, been systematically studied. However there are uncontrolled studies that suggest transplantation is a treatment option in acute fulminant liver failure secondary to HEV.[12] A recent study has evaluated the safety and efficacy of an HEV recombinant protein vaccine in a phase 2, randomized, double-blind, placebo-controlled trial and demonstrated a small benefit in those at high risk of developing acute HEV infection.[13]

Conclusion

This case demonstrates that acute UK acquired HEV is an important, albeit rare, cause of fulminant liver failure, which has a significant mortality. Thus, clinicians should routinely test for HEV serology in patients with acute hepatitis.

References

1 Aggarwal R, Naik S. Epidemiology of hepatitis E: current status. *J Gastroenterol Hepatol* 2009;**24**:1484–93
2 Turner J, Green J. Hepatitis E: a UK perspective. *Br J Hosp Med (Lond)* 2008;**69**:517–19
3 Romano L, Paladini S, Tagliacarne C, Canuti M, Bianchi S, Zanetti AR. Hepatitis E in Italy: a long-term prospective study. *J Hepatol* 2011;**54**:34–40
4 Bendall R, Ellis V, Ijaz S, Thurairajah P, Dalton HR. Serological response to hepatitis E virus genotype 3 infection: IgG quantitation avidity, IgM response. *J Med Virol* 2008;**80**:95–101
5 Sadler GJ, Mells GF, Shah NH, Chesner IM, Walt RP. UK acquired hepatitis E–An emerging problem? *J Med Virol* 2006;**78**:473–5
6 Levine DF, Bendall RP, Teo CG. Hepatitis E acquired in the UK. *Gut* 2000;**47**:740
7 Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* 2008;**8**:698–709
8 Banks M, Grierson S, Fellows HJ, Stableforth W, Bendall R, Dalton HR. Transmission of hepatitis E virus. *Vet Rec* 2007;**160**:202
9 Banks M, Martelli F, Grierson S, *et al.* Hepatitis E virus in retail pig livers. *Vet Rec* 2010;**166**:29
10 Meader E, Thomas D, Salmon R, Sillis M. Seroprevalence of hepatitis E virus in the UK farmingpopulation. *Zoonoses Public Health* 2010;**57**:504–9
11 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

12 Ohnishi S, Kang JH, Maekubo H, Takahashi K, Mishiro S. A case report: two patients with fulminant hepatitis E in Hokkaido Japan. *Hepatol Res* 2003;**25**:213–18

13 Shrestha MP, Scott RM, Joshi DM, *et al.* Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007;**356**:895–903