Hepatitis E, A and other hepatotropic viruses

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Abstract

Hepatotropic viruses are extremely common worldwide and among frequent causes of acute hepatitis and acute liver failure. Most commonly, these infections present with a viral prodrome and an acute increase in liver enzymes but atypical presentations can occur. Whereas most infections are benign and self-limiting, chronic states do occur; in the case of Epstein–Barr virus and cytomegalovirus, latency occurs after primary infection, with reactivation occurring at later times of illness. Vaccination programmes for hepatitis A, where available, have led to a significant reduction in incidence. Our knowledge of these viruses continues to expand, especially with regard to hepatitis E and its genotypes. Hepatitis E virus has recently been found in donated human blood and is the causative agent in some patients presenting with neurology signs and symptoms; it is now considered a significant health burden in both developing and developed countries.

Keywords Cytomegalovirus; emerging infections; Epstein–Barr virus; hepatitis A; hepatitis E; MRCP; seronegative hepatitis; viral hepatitis; zoonosis

Introduction

Hepatotropic viruses are the most common cause of liver disease worldwide and represent a significant burden in terms of public health, healthcare costs and patient mortality and morbidity. In the developing world, hepatitis A and E are among the most common causes of acute liver failure (ALF), and worldwide hepatitis E is the most common cause of acute hepatitis.

Hepatitis E virus (HEV)

HEV is an RNA virus with eight genotypes. In 2005, the global burden of disease was estimated at 3.4 million symptomatic cases; [1] however, this study covered only part of the developing world and did not take account of the surprisingly large numbers of cases of locally acquired hepatitis E in developed countries.

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Key points

- Hepatitis E virus (HEV) is common in developed countries, usually resulting in asymptomatic or pauci-symptomatic illness
- Patients with underlying chronic liver disease have an adverse outcome when infected with HEV, and chronic infection occurs in the immunosuppressed
- HEV can present with neurological symptoms with minimal increase in liver enzymes
- HEV causes iatrogenic infection via blood products, and all UK blood donors are now screened for HEV
- Epstein–Barr virus (EBV) often presents with a triad of hepatitis, splenomegaly and lymphocytosis
- Seronegative hepatitis is often an acute self-limiting illness in a non-transplant setting
- A hepatitis A vaccine is available and has resulted in a dramatic decline in reported infection rates

Hepatitis E in developing countries

In developing countries in Asia and Africa, hepatitis E is caused by HEV genotypes 1 and 2, which are obligate human pathogens spread orofaecally by infected water. Infections occur sporadically and in large outbreaks, sometimes involving tens of thousands of cases, and are seen in locations with poor sanitary infrastructure, such as African refugee camps, and India and Nepal. Hepatitis E causes a brief self-limiting hepatitis in young adults. For unknown reasons, the mortality in pregnant women is 25%, and patients with underlying chronic liver disease also have a poor prognosis, with mortality rates up to 70% (see Dalton et al., 2008 in Further reading)

Hepatitis E in developed countries

Hepatitis E was previously thought to be uncommon in developed countries and usually seen only in travellers returning from endemic areas, but this has now been shown to be incorrect.

Seroprevalence: this is a means of determining the burden of infection in a population over time. Early anti-HEV immunoglobulin (Ig) G seroprevalence studies showed rates of <5%. However, the assays used were of poor sensitivity, and this led mistakenly to the notion that HEV was not a significant health issue in developed countries. More recent studies, using a highly sensitive assay, show much higher seroprevalence rates: Scotland 4.6%, South-West England 16%, Holland 27%, and 52% in South-West France. These higher rates suggest that HEV is endemic in many developed countries, and are more congruent with the high incidences of HEV viraemia in blood donors (see below).[2]

Incidence: there are an estimated 100,000 infections per year in England, and HEV is now the most common cause of acute viral hepatitis in several developed countries (Table 1). The incidence

Causes of jaundice and a serum ALT >400 IU/litre

	Incidence[a]	Comments
Drug-induced liver injury	16%	• Common in elderly individuals • Must exclude other cases of hepatocellular injury • Diagnosis not secure without testing for HEV
Liver metastases	10%	• Significant weight loss usually seen
Autoimmune hepatitis	5%	• Can sometimes be difficult to differentiate from HEV when autoantibodies are negative • Occurs mainly in women (F:M = 3:1)
Acute HEV	5%	• Affects mainly middle-aged/elderly men • ALT 1500 IU/litre, with a wide range
Seronegative hepatitis	3%	• Negative for causes of acute viral hepatitis • Occurs at all ages • Possibly caused by an unidentified hepatotropic virus
Epstein–Barr virus	3%	• Occurs at all ages, including elderly individuals • Mild hepatitis with a 'mixed' liver function test picture • <10% have symptoms of infectious mononucleosis • 95% have a combination of hepatitis, splenomegaly and lymphocytosis
Acute HBV	2%	• ALT is usually higher than in HEV
HAV	1%	• ALT is usually higher than in HEV • Intrafamilial spread is common
Acute HCV	<1%	• Very uncommon
Cytomegalovirus	<1%	• Very uncommon

[a] Incidence refers to the percentage of individuals with each diagnosis from a cohort of >1000 consecutive patients with hepatocellular jaundice presenting to a rapid-access jaundice clinic, Cornwall, UK 1998–2014.

Table 1

varies between and within countries: in the USA it is 0.7%, in Holland 1.1%, in South-West France 3.2% and in the UK 0.2%. It is particularly common in South-West France and is considered hyperendemic in the Toulouse area.[2]

Source and routes of infection: in developed countries, locally acquired hepatitis E is caused by genotypes 3 and 4, which are porcine zoonoses (Figure 1). Pig herds worldwide are asymptomatically infected, with genotype 3 being found in every step of pork production from pig farms to meat consumables on sale. An important route of human infection is consumption of uncooked or undercooked pork products. Unlike hepatitis A, person-to-person spread within households is not a significant route of infection.[2]

Acute hepatitis E: around 95% of infections are asymptomatic. Only a small minority develop symptomatic hepatitis, which for unknown reasons occurs mainly in middle-aged and elderly men. An incubation period of 2–6 weeks is followed by symptoms indistinguishable from any other acute viral hepatitis (Table 2); 5–10% of patients present with neurological symptoms. Jaundice and hepatomegaly are present in the majority. Most recover within 4–6 weeks, but individuals with underlying chronic liver disease can have a more severe illness and higher mortality rate. In contrast to developing countries, excess mortality is not seen in pregnant women infected with genotypes 3 and 4.[2]

Chronic hepatitis E: In immunosuppressed individuals (transplant recipients, patients with haematological malignancy or HIV), infection with HEV genotype 3 and 4 can become chronic. Sixty per cent of immunosuppressed transplant recipients who are exposed fail to clear HEV, resulting in chronic infection.[3] Such patients usually have no symptoms, no jaundice and only a modest increase (100–300 IU/litre) in serum alanine aminotransferase (ALT). It is an easy diagnosis to overlook (Table 3), but one that is important to make as untreated disease is rapidly progressive and 10% of patients develop cirrhosis within 2 years. The prevalence in transplant centres in Europe varies, ranging between 1% and 3.2%. Resolution of infection is confirmed by absence of virus being excreted in stool after clearance from blood and this test can guide ribavirin therapy duration.

Extrahepatic manifestations

Acute and chronic hepatitis E can cause several extrahepatic manifestations, including thrombocytopenia, cryoglobulinaemia, glomerulonephritis, acute pancreatitis, acute thyroiditis and a range of neurological syndromes. Neurological manifestations occur in 5–8% of patients,[4] dominating the clinical picture in association with generally non-severe hepatitis and no jaundice. Recent studies have shown that HEV is the infective trigger in 5% and 10% of cases of Guillain–Barré syndrome and brachial neuritis, respectively. The range of neurological illness associated with HEV continues to expand and includes transverse

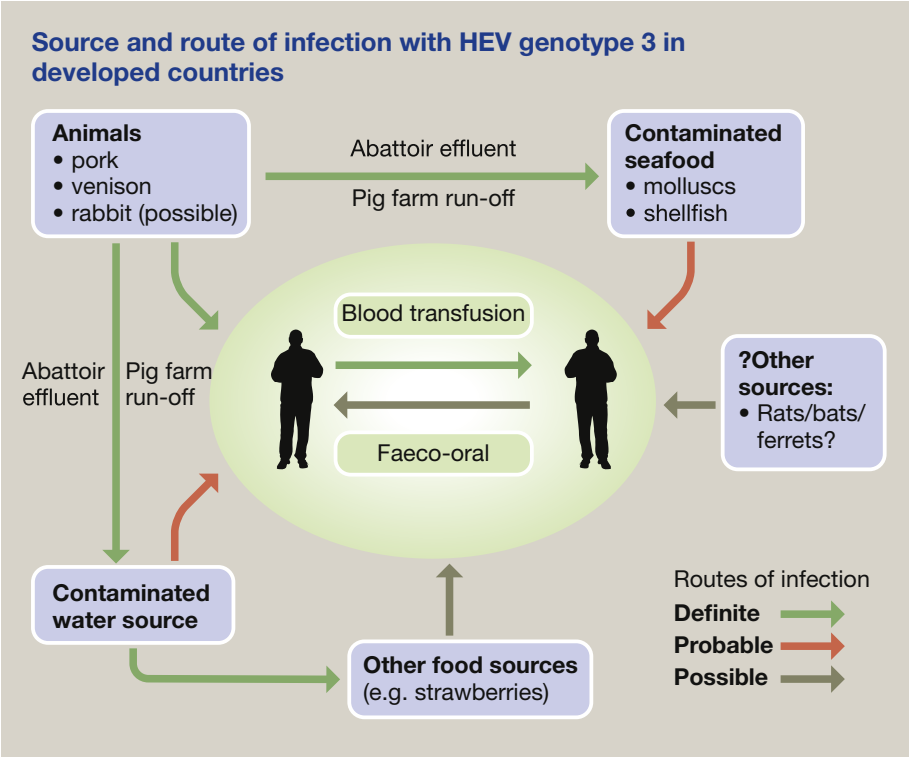

Figure 1

myelitis, Bell's palsy, vestibular neuritis, encephalitis, myasthenia gravis and peripheral neuropathy.

Investigations

Diagnosis is based on a combination of a raised anti-HEV IgM, rising IgG and positive RNA polymerase chain reaction (PCR). After acute infection, anti-HEV IgM rises very quickly and stays positive for 3–6 months, whereas IgG is slower to rise and usually remains positive for years. In acute infection, HEV RNA can be detected in both serum and stool for several weeks from symptom onset and remains positive in chronic infection. Serology can be unreliable in immunosuppressed individuals so PCR is the key investigation.

Who should be tested for HEV?

Recent European guidelines recommend that hepatitis E should be tested in all patients with acute hepatitis as part of the initial diagnostic work-up.[3] The travel history is irrelevant (see Table 1 for the differential diagnosis). A common error is to diagnose drug-induced liver injury without testing for and excluding hepatitis E infection (see Dalton et al. 2007 in Further reading).

Clinicians should have a low threshold for testing for HEV in patients with acute neurological syndromes and abnormal liver function tests, and in immunosuppressed individuals with persistently elevated ALT concentrations (always including PCR; see above).

Symptoms of acute hepatitis E infection[4]

Common	Less common
• Jaundice	• Pruritus
• Anorexia	• Weight loss
• Lethargy	• Headaches
• Abdominal pain	• Arthralgia
• Vomiting	• Neurological (5–8%)
• Fever	• No symptoms
• Myalgia	

Table 2

HEV and donated blood

As hepatitis E is so commonly asymptomatic, it is no surprise that HEV has found its way into the supply of donated human blood, but the incidence of HEV viraemia in donated blood is surprisingly high (Table 4).[5] Screening for HEV in UK blood donors using HEV RNA was initiated in 2016 with overall positivity rates of around 1 in 3000. The incidence of such transfusion-related events has been estimated at 1000 per year in England prior to the introduction of screening, with documented adverse outcome, particularly in the immunosuppressed. Blood donor screening for HEV has also commenced, or is being considered, in several other developed countries (Table 4).

Treatment and prevention

Acute HEV is mostly self-limiting and usually requires no treatment. A few patients with severe and/or neurological illness have been treated successfully with ribavirin monotherapy. In chronic infection, the first step is, if possible, to reduce the level of immunosuppression, which clears HEV infection in 30% of cases. If this fails or is not possible, ribavirin monotherapy for 3 months usually achieves viral clearance.

Differential diagnosis of serum ALT 100–300 IU/litre in immunosuppressed transplant recipients

Diagnosis	Comments
Graft rejection	• Common early cause of increased liver enzymes • Late episodes occur in the context of low immunosuppression levels
Drug-induced liver injury	• **Must** exclude other cases of hepatocellular injury
Recurrence of original liver disease	• Autoimmune • Chronic HBV • Chronic HCV
Graft-versus-host disease	• Bone marrow/stem cell transplants
Intercurrent infection	• Respiratory • Urinary
Sepsis	• Bacterial • Fungal
Viral infections	• Chronic HEV • Epstein–Barr virus • Cytomegalovirus • Other (including adenovirus, herpes simplex virus, varicella-zoster virus)

HAV, hepatitis A; HBV, hepatitis B; HCV, hepatitis C.

Table 3

There is a safe and effective vaccine for HEV but it is currently licensed for use only in China. It is uncertain when this will become more widely available. Other strategies for prevention are more problematic owing to the ubiquitous nature of HEV in diverse animal species, the environment and the human food and blood supply (Figure 1).

Hepatitis A virus

HAV, an RNA virus, causes an acute hepatitis with significant morbidity and infrequent mortality worldwide. It is spread via the faecal-oral route and has its highest incidences in areas with low levels of sanitation and poor hygiene. Cases occur in a sporadic or an epidemic form that can on occasions be traced back to a single food source.

HAV-related infection is usually a benign and self-limiting condition; however, it has a clinical course ranging from mild and asymptomatic infection to fulminant hepatic failure and death or a need for liver transplantation. The risk of a severe outcome is highest in very young and elderly individuals and individuals with underlying chronic liver disease or viral co-infections. The most common presentation is of a viral prodrome followed by jaundice, pruritus, dark urine and pale stools; jaundice occurs in 70% of cases and hepatomegaly in 80%.

Diagnosis is based on positive HAV IgM antibodies. HAV IgG antibodies appear early in the recovery period and remain detectable for decades; infection results in life-long immunity. There is no specific treatment for HAV infection and management is supportive, liver transplant being required only in severe cases. Prognosis is good, with nearly all patients having a complete recovery by 6 months and most recovering much sooner. A small number run a relapsing or cholestatic course but all still make a full recovery and there is no chronic HAV carrier state. A highly effective vaccination against HAV is available and has resulted in a dramatic decline in reported infection rates (see Wasely in Further reading).

Epstein–Barr virus (EBV)

EBV is extremely common, with a seroprevalence of 90–95% worldwide. Most infections occur in childhood and are asymptomatic. Symptomatic disease usually presents in young adults with infectious mononucleosis, who experience the triad of fever, sore throat and lymphadenopathy. The associated hepatitis is normally a subclinical transaminitis. Hepatological manifestations of EBV infection range from mild hepatitis, which is common, to the rare occurrence of life-threatening ALF occasionally requiring liver transplant. EBV-related hepatitis was previously regarded as a complication of infectious mononucleosis, but more recently has been described in patients without clinically apparent infectious mononucleosis, as well as in elderly

HEV viraemia in blood donors and donor screening status

Country	Number of blood donors HEV RNA positive	Study and date	Current status of blood donor screening for HEV
England	1:2848	Hewitt et al., 2014	Universal screening since 2017
Scotland	1: 2481	Thom et al., 2018	Universal screening since 2017
France	1:2218	Gallian et al., 2014	Screening of donations for pooled plasma components 2013 Universal screening under consideration
Germany	1:1200	Vollmer et al., 2012	Universal screening starts 2020
Ireland	1:4997	O'Riordan et al., 2016	Universal screening since 2016
Japan (Hokkaido)	1:8173	Matsubayashi et al., 2011	Universal screening since 2005
Netherlands	1:2671	Slot et al., 2013	Universal screening since 2017
Poland	1:2109	Grabarczyk et al., 2018	Screening under consideration
Denmark	1:2330	Harrishøj et al., 2016	Screening has been deemed unnecessary

Table 4

populations (see Vine et al. in Further reading). Cholestasis and jaundice have also been documented.

The diagnosis of EBV hepatitis is suggested by the triad of hepatitis, splenomegaly and lymphocytosis (present in 95% of patients; Table 1), and is confirmed by the presence of anti-EBV IgM, with EBV IgG representing previous infection. EBV DNA can also sometimes be detected. No treatment is usually required, although antiviral agents such as ganciclovir and valganciclovir have been shown to be effective in some severe infections or in immunocompromized individuals.

Cytomegalovirus (CMV)

CMV has a worldwide seroprevalence of 40–100%. It has a broad clinical phenotype, depending on the patient's underlying immune status. In immunocompetent patients, most CMV infections are subclinical or mild, but a small percentage present with a mononucleosis-type syndrome with a mild or subclinical hepatitis. Uncommon hepatological manifestations of CMV infection include acute hepatitis, hepatomegaly, granulomatous hepatitis, jaundice, cholestatic hepatitis and ALF. Portal vein thrombosis is a rare complication of acute CMV hepatitis (see Gallegos in Further reading). After primary infection CMV persists in the latent form, which can reactivate during later episodes of illness or infection.

Severe CMV infection occurs in immunocompromized patients (transplant recipients, patients with HIV) and can infect multiple organs, not just the liver. This causes a spectrum of conditions including retinitis, encephalitis and pneumonitis.

The diagnosis of acute CMV infection is made with positive CMV IgM antibodies and positive CMV DNA on PCR. IgG antibodies are produced several weeks later and persist for years. Treatment is usually with valganciclovir or ganciclovir.

Seronegative hepatitis

Seronegative hepatitis is a well-recognized cause of ALF requiring liver transplantation and is one of most common indications for liver transplantation in patients presenting with ALF. The aetiology is unknown, but hypotheses include an unidentified hepatotropic virus, an unidentified autoimmune condition or immune dysregulation triggered by an unknown pathogen. Patients should be diagnosed with seronegative hepatitis only if they have a negative history for medications which can cause liver injury (including non-prescription/herbal medications and supplements), and after a full negative chronic liver disease screen; this should include viral markers for hepatitis A–E, EBV, CMV, liver autoantibodies and immunoglobulins.

The outcome in patients with seronegative ALF without liver transplantation is poor. However, a spectrum of severity occurs; patients with seronegative hepatitis presenting to a non-transplant centre mostly had self-limiting disease. The proportion of patients with true seronegative hepatitis who develop ALF is not known. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 53-year-old man presented with a 2-week history of jaundice, lethargy and weakness of both legs. He had a history of type 2 diabetes and hypertension but was stable on treatment. There was no history of foreign travel. On clinical examination he was moderately jaundiced but there were no other significant findings

Investigations

- Bilirubin 230 micromol/litre (1–22)
- Alanine aminotransferase (ALT) 2500 U/litre (5–35)
- Aspartate transaminase (AST) 1990 U/litre (1–31)
- alkaline phosphatase 126 U/litre (45–105)
- Albumin 39 g/litre (37–49)

What is the most likely diagnosis?

A. Hepatitis A
B. Drug-induced liver injury
C. Hepatitis E
D. Autoimmune hepatitis
E. Ischaemic hepatitis

Question 2

A 58-year-old woman presented for review. She had end-stage renal disease and had two renal transplants (the last was 4 years previously). She had had no new medicines or recent medical interventions.

Investigations

- Bilirubin 20 micromol/litre (1–22)
- ALT 114 U/litre (5–35)
- AST 139 U/litre (1–31)
- Alkaline phosphatase 69 U/litre (45–105)
- Albumin 42g/litre (37–49)
- Hepatitis E virus RNA (viral load) (100,000 copies/ml)

What should the initial management be?

A. Reducing immunosuppression
B. Ribavirin therapy
C. Interferon-α therapy
D. Tenofovir therapy
E. Sofosvobir therapy

Question 3

A 21-year-old medical student from the UK is planning to travel to India for a period of elective study. Which one of the following vaccines is she most likely to require prior to her trip?

A. Hepatitis B
B. Hepatitis A
C. Hepatitis E
D. Yellow fever
E. Epstein–Barr virus