Hepatitis E virus in developed countries: one of the most successful zoonotic viral diseases in human history?

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Abstract

Until recently, hepatitis E was thought to be largely confined to hyperendemic areas in Asia, Africa and Mexico. Over the last 10 years it has become clear that this is not the case, as it is surprisingly common in developed countries. In these settings, it is caused by HEV genotypes 1 and 2, which are obligate human hepatotropic RNA viruses causing acute and chronic hepatitis, and a spectrum of neurological injury. HEV RNA has been found in donated blood from an increasing number of countries, and in some locations with a very high incidence. The clinical phenotype and burden of disease in humans is still emerging. In contrast to previous ‘received wisdom’, zoonotically transmitted HEV may be one of the most successful zoonotic viral infections in human history. How did we, as a scientific community, get this so badly wrong? This review considers this question from a largely clinical perspective, explores the places HEV has been ‘hiding’ and the emerging clinical phenotype in humans.

Keywords: hepatitis E virus (HEV), hepatitis, zoonosis, neurological injury, blood products

Hepatitis E in developing countries

For many years hepatitis E virus (HEV) was thought to be largely confined to the developing world where it is a major health issue often causing large outbreaks. In such settings hepatitis E is caused by HEV genotypes 1 and 2, which are obligate human pathogens spread orofaecally via contaminated water supplies [1,2]. It mainly affects young adults with a self-limiting illness, except in pregnant women where fulminant hepatic failure can occur, with a high mortality rate [3].

A recent study has estimated that in nine of 21 global burden of disease (GBD) regions, there are 3.4 million symptomatic cases of hepatitis E each year, with 70,000 deaths and 3,000 stillbirths [4]. This is almost certainly an underestimate of the GBD, as there may be up to 1,000 HEV-related maternal deaths per annum in Bangladesh alone [5]. In addition, recent studies suggest that anti-HEV seroprevalence estimates (on which the GBD was partly calculated) may have lacked sensitivity, and underestimated the true seroprevalence by 50% (unpublished observations).

Hepatitis E in developed countries

Following the discovery of HEV in the 1980s in developed countries, hepatitis E was thought to be a disease seen only in travellers returning from endemic areas in the developing world. Hepatitis E was considered exceedingly rare and of little relevance. Conceptually, the virological and hepatological features of HEV were considered analogous to hepatitis A virus (HAV): both being orofaecal hepatotropic RNA viruses causing acute self-limiting hepatitis. These misguided notions unfortunately remained the ‘received wisdom’ for the best part of 20 years [6].

Acute hepatitis E

We have been studying HEV in southwest England for over 10 years [6–21]. In epidemiological terms, this is an ideal setting to study an autochthonous disease such as hepatitis E owing to: (a) its geographical isolation; (b) the very low number of immigrants born overseas (crucial in the context of study of locally acquired infection); (c) a very limited number of secondary care providers; and (d) the existence of rapid-access jaundice clinics (the Jaundice Hotline Clinic, JHL) [22].

The JHL has proven to be an invaluable tool for studying the epidemiology and clinical features of acute autochthonous hepatitis E, as most patients developing acute jaundice/hepatitis in our community are reviewed via the JHL, and laboratory and clinical outcome data are prospectively recorded [23–25]. Initially we noted that, despite appropriate investigation, there were a number of patients with hepatitis for whom we had no diagnosis (Figure 1). Such patients were retrospectively and then prospectively tested for HEV. Recent analysis shows that autochthonous hepatitis E accounts for 5% of patients presenting with hepatocellular jaundice to the JHL (Figure 2), and is the commonest cause of acute hepatitis in southwest England by quite a margin (Table 1) [23–25].

We have now carefully documented over 100 cases of acute autochthonous hepatitis E [26]. All were caused by HEV genotype 3, when sequencing was possible. Remarkably, and uniquely, acute hepatitis E appears to have a predilection for middle-aged/elderly males [1], with a male:female ratio of 3.2:1 and a median age of 63.5 years [26]. Acute hepatitis E caused by genotype 3 (and genotype 4 in China, Japan and a few recently described clusters in Europe) [27,28] has been found in every single developed country in which it has been sought. All these studies have described very similar demographics, with an excess
of cases in older men [13,14,29–33]. The reasons for these observations are uncertain.

The symptoms of hepatitis E infection are similar to those seen in any form of viral hepatitis (Table 2) [26], except in a minority of patients who present with a primarily neurological illness (see later). A number of other extra-hepatic manifestations have been described (Table 3) [20,26,34–37]. In contrast to HEV genotype 1, excess mortality in pregnant women is not seen with genotype 3, and the few women who have been described in the literature have all survived [38]. The majority of patients have a self-limiting illness, with clinical and biochemical recovery within a few weeks. A minority have a more severe hepatitis, and some patients (3.8% in our recent series) [26] die from subacute liver failure [16,19,21,39]. Such patients usually have underlying chronic liver disease [19,40].

Table 1. Causes of acute viral hepatitis

| Incidence* Comments (%) |       |
|------------------------|-------|
| HEV                    | 5     |
| Affects predominantly middle-aged and elderly males |
| Seronegative hepatitis [24] | 3     |
| Negative for all known causes of acute viral hepatitis |
| Occurs at all ages, including adolescents |
| May be caused by an as yet unidentified hepatotropic virus |
| EBV [25] | 3     |
| Surprisingly common, occurs at all ages |
| Mild hepatitis, but can be severe in elderly |
| <10% have symptoms of infectious mononucleosis |
| Diagnosis suggested by a combination of hepatitis, splenomegaly and lymphocytosis, which is present in 95% |
| HBV                    | 2     |
| ALT is usually higher (3–500 IU/L) than in HEV |
| HCV                    | <1    |
| Very uncommon |
| CMV                    | <1    |
| Very uncommon |

* Incidence refers to the percentage of individuals with each infection from a cohort of 1,054 consecutive patients presenting to the JHL Clinic, Cornwall, UK 1998–2014.

Hepatitis E; HAV: hepatitis A; HBC: hepatitis B; HCV: hepatitis C; CMV: cytomegalovirus; EBV: Epstein–Barr virus; ALT: alanine transaminase.

Studies of acute HEV genotype 1 infection in patients with chronic liver disease in Asia show a mortality rate of up to 70% [41]. A prospective UK/French study of 372 patients with decompensated chronic liver disease and HEV genotype 3 showed a mortality rate of 27% (Blasco-Perrin et al., personal communication). The incidence of hepatitis E in the context of chronic liver disease varies significantly by geographical location, and was much more common in southwest France (7.9%) than in the UK (1.1%). There appears to be no clinical or laboratory clues to diagnosis at presentation, and so patients with decompensated chronic liver disease should be considered for routine HEV testing, particularly in high incidence areas. An early diagnosis is important, as patients with chronic liver disease who have decompensated due to HEV infection have been successfully treated with ribavirin [19].

Chronic hepatitis E

The field of hepatitis E was changed for ever by the description of chronic infection in transplant recipients in two side-by-side papers from southern France published in the New England Journal of Medicine in 2008 [42,43]. Typically patients have no symptoms, they are not jaundiced and their alanine aminotransferase (ALT) runs between 200 and 300 IU/L. Chronic infection occurs in approximately 60% of solid organ transplant recipients exposed to HEV genotype 3 infection [44]. Progressive liver disease is common and is usually more rapid than that seen in chronic infection with HBV or HCV and 10% of recipients with chronic hepatitis E infection are cirrhotic within 2 years [44,45]. The prevalence of chronic hepatitis E in the European transplant population averages between 1% and 2% [46,47]. The figure is much higher in the transplant centres in southwest France [44].
Chronic hepatitis E infection can also occur in other immunosuppressed groups, including patients with haematological malignancy [48] and in individuals with HIV infection [12]. In the latter group, HIV/HEV chronic co-infection is uncommon, and is only seen in patients who are profoundly immunosuppressed with CD4 cell counts <250 cells/μL. So far chronic infection has only been described with HEV genotype 3 [49].

Treatment and prevention

Case reports and case series show that chronic hepatitis E infection can be treated with the antiviral agents ribavirin and/or interferon. Most published data concern treatment of chronically infected solid-organ transplant recipients with ribavirin. The suggested treatment algorithm is shown in Figure 3 [50]. Acute infection generally requires no treatment, as it is usually a self-limiting illness. A few cases of severe hepatitis have been treated successfully with ribavirin (see above) [21].

A safe and effective vaccine has now been licensed for use in China [51]. It is not known whether it will be licensed for use in other countries.

Epidemiology

The incidence of hepatitis E infection varies between and also within countries. The incidence in the USA is 0.7% [52], the Netherlands 1.1% [53] and in southwest France it is as high as 3.2% [54]. In the UK, the incidence is 0.2% [2]. As in France, where infection is more common in the south of the country, significant regional variation in the UK also occurs. There appears to be far more circulating virus in England than Scotland, reflected by anti-HEV IgG seroprevalence rates in blood donors of 12% and 4.6%, respectively [55,56] and congruently higher rates of viraemic blood donors in England [57]. Why there is such a regional variation within these countries is not known.

Each year it is estimated that in England there are 100,000 infections with HEV [57]. In 2013 there were just 691 laboratory confirmed cases [58], suggesting that most infections are either asymptomatic or unrecognised (Figure 4). In contrast with HEV genotype 1 where the ‘clinical attack rate’ is 50%, with zoonotic infection with HEV genotype 3.

The clinical spectrum of Figure 4. The clinical spectrum of infection with HEV genotype 3. Most cases are asymptomatic; however, many are symptomatic, but not recognised.
post-infection) sera from PCR proven cases from southwest England [10]. The Chinese assay had a sensitivity of 98%, compared to 56% for the Genelabs assay. When applied to a population of blood donors the Genelabs assay underestimated the seroprevalence by a factor of four. The Chinese assay was subsequently applied to a population of blood donors in southwest France and the seroprevalence estimate increased from 16% to 52% with the more sensitive assay [71].

Sceptics have argued that a seroprevalence of 52% in Toulouse blood donors cannot possibly be correct, and that the result is due to lack of assay specificity. This is very unlikely to be true, as the seroprevalence in children aged 2–4 from the same population is low (2%) [71]. In addition, a seroprevalence of 52% is entirely congruent with the high incidence of primary and re-infections with hepatitis E documented in this community, both in transplant recipients [53] and asymptomatic blood donors [72]. These data suggest that much of the early literature is flawed, as assays of poor sensitivity have grossly underestimated the true seroprevalence, so enabling HEV to ‘hide’ at population level. More recent studies with the Chinese assay have shown much higher estimates than previously, with seroprevalence rates that are compatible with rates of HEV viraemia in asymptomatic blood donors (Table 4) [53,55–57,69–81].

Transplant recipients

Chronic hepatitis E infection in transplant recipients is clinically ‘silent’, as patients have no symptoms. The only clue to the diagnosis is a very modest elevation in serum ALT (100–300 IU/L) [1]. It is a diagnosis that is easily overlooked. How long has HEV been ‘hiding’ in transplant patients? This is unknown, but probably since the advent of transplantation in the late 1960s.

Drug-induced liver injury (DILI)

HEV can also masquerade as drug-induced liver injury (DILI). Some years ago we studied patients with criterion-referenced DILI and found that in six of 47 patients (13%) we had made a diagnostic error, as their illness was not due to DILI, but infection with HEV genotype 3 [18]. This is an easy diagnostic error to make, as both DILI and HEV genotype 3 infection are common in the elderly.

Neurological illness

Over recent years there have been quite a few case series and reports describing HEV-associated neurological illness. There appears to be a very wide spectrum of reported neurological injury that includes Bell’s palsy, encephalitis, vestibular neuritis, small fibre peripheral neuropathy, Guillain–Barré syndrome and brachial neuritis [20,26]. In some cases HEV RNA has been found in the cerebrospinal fluid. The pathogenic mechanisms are unknown.

Guillain–Barré syndrome is a post infectious immune-mediated polyradiculopathy triggered by Campylobacter in 35% of cases but with an unknown aetiology in 50% of cases. In a prospective longitudinal study in 100 patients in the mid–1990s, the Dutch Guillain–Barré Study Group, found that 30% of patients had unexplained mildly abnormal liver function tests (LFTs) at the start of the neurological illness [82]. A recent case control study of 201 patients with Guillain–Barré syndrome from the Netherlands showed that 5% of patients (n = 10) had evidence of hepatitis E infection at the start of their neurological illness [83] and of these, three patients (1.5%) were viraemic with HEV genotype 3 at presentation. This has raised the question of whether these patients might benefit from early treatment with ribavirin therapy.

What about the other 25% of patients with Guillain–Barré syndrome and abnormal LFTs? Could these cases have also been triggered by HEV? One possible explanation could be that these cases might have been triggered re-infection with HEV. If the re-infection with HEV was 1 or 2 months before the neurological symptoms started, it would be very difficult to make a diagnosis. Such patients would be IgM negative (typical of re-infection), HEV PCR negative (the viraemic ‘window’ lasts only a few weeks), but IgG positive. Thus, the only way of distinguishing recent re-infection from distant past infection would be to demonstrate a rising IgG. This is problematic in this cohort of patients, as many are treated with intravenous immunoglobulin, which may well interfere with the IgG result on the convalescent blood sample.

A further Anglo-Dutch cohort study of 47 patients with brachial neuritis showed that 10% (n=5) had evidence of hepatitis E infection at the onset of neurological symptoms [84]. In contrast to other triggers of brachial neuritis, HEV-associated cases had bilateral neurological symptoms, sometimes with phrenic nerve involvement. Following this study, a brachial neuritis registry has been established in southwest England, with several further HEV-associated cases documented in just a few months (unpublished observations). A similar registry is being established in the Netherlands.

In both the above studies, neurological symptoms and signs dominated the clinical picture: patients were anicteric, the ALT was only mildly elevated (typically <600 IU/L), and occasionally normal. This led the lead neurologist to pose the following question: ‘Is it possible that hepatitis E has been misnamed? These patients have profound neurological illness, but not much
of a hepatitis!' This is an interesting question. The first step in the process of addressing this issue is about to start: a UK-Dutch-French multinational study of all patients with non-traumatic neurological injury who will be systematically tested for HEV at presentation. The results are awaited with interest.

**Current diagnostic testing algorithms**

In the UK, and in most of the rest of Europe, current diagnostic testing algorithms suggest that patients presenting with acute hepatitis should first be tested for HAV, HBV and HCV. If these tests are negative, then testing for HEV should be considered [85]. This approach is outdated, and means that the diagnosis of hepatitis E is either delayed, or missed altogether.

As hepatitis E is the commonest cause of acute viral hepatitis (Table 1, Figure 2) [24,25], it would make much more sense to first test all patients for HEV, and if this is negative then consider testing for HAV, HBV and HCV. How should we define ‘hepatitis’? Preliminary data from southwest England suggests that testing patients with an ALT >400 IU/L or with an ALT/alkaline phosphatase ratio >6 times the upper limit of normal has quite high sensitivity and specificity for HEV diagnosis. Patients with Guillain–Barré syndrome and brachial neuritis should be tested for HEV irrespective of the ALT result. In addition, clinicians should have a low threshold for testing patients with unexplained neurological symptoms and abnormal LFTs. Immunosuppressed patients with persistently abnormal LFTs should be tested for HEV to exclude chronic infection. This should include PCR as well as serology, as the latter is less accurate in the immunosuppressed.

**Blood supply**

One of the potentially most worrisome places that HEV has been ‘hiding’ is in human blood products used for transfusion. Given that zoonotically acquired hepatitis E is very commonly asymptomatic, it comes as no surprise that HEV has found its way into the blood supply. What has astonished some observers is the very high incidence of HEV viraemia in the donor population (Table 4) [53,55–57,69–81]. Transmission of HEV via blood products is currently occurring as donors are not screened, and there are increasing numbers of reports of both acute and chronic infection in recipients (Table 5) [57,86–97].

In southeast England, a recent study demonstrated HEV RNA-positive plasma pools in 0.04% of donor samples, with one in 2,848 donors having HEV (genotype 3) viraemia at the time of donation [57]. Retrospective analysis showed that blood components were given to 60 patients, 43 of whom were available for follow-up: the overall transmission rate of HEV was 42%, and infection was significantly more common from high viral-load donations and plasma-based blood products, and less likely if the donor sample contained anti-HEV antibodies. ‘Classical’ post-transfusion hepatitis was uncommon in infected recipients, with only one in 18 developing clinically apparent post-transfusion hepatitis. This is not so different from the ‘clinical attack rate’ seen in individuals infected orofaecally. Seven of 10 immunocompromised patients infected were viraemic at 3 months following exposure, which is the working definition of chronic infection with HEV (see above). Two were treated with antiviral agents. There were four deaths, three of which were from unrelated causes. With a prevalence of one in 2848 in this study, a projection across England leads to an estimated 100,000 infections and a total of 1,200 HEV-contaminated transfusion events in the year of the study [57].

### Table 5. Transfusion-transmitted HEV infection

| Country, Year | Ref | Number of infections / exposed | Comments |
|---------------|-----|-------------------------------|----------|
| UK, 2014      | [57] | 18 / 43                       | Retropective study of 43 transfusion episodes available for investigation, 18 patients developed HEV |
| France, 2014  | [86] | 5                             | Immunosuppressed transplant recipients treated with plasmapheresis with Intercept-treated plasma. Both developed asymptomatic chronic infection requiring ribavirin therapy |
| Japan, 2014   | [87] | 2                             | Immunosuppressed patient (myelodysplastic syndrome), received packed red cells from HEV-positive donor. Clinical hepatitis. Patient died from an unrelated cause (lung abscess) |
| Japan, 2014   | [88] | 1                             | Immunocompetent patient, received HEV-contaminated platelet transfusion and developed post-transfusion acute hepatitis |
| France, 2013  | [89] | 1                             | Immunocompetent liver transplant recipient received HEV-contaminated packed red cell transfusion. Developed post-transfusion acute hepatitis. HEV cleared with ribavirin |
| Germany, 2013 | [90] | 1                             | Six blood products identified from one donor. Retropective study: |
|               |     |                                | • Three patients died (no follow up). |
|               |     |                                | • One immunocompromised patient – chronic infection |
|               |     |                                | • One immunocompetent child – probably acute infection |
|               |     |                                | • One immunocompromised patient did not contract HEV |
| France, 2012  | [91] | 1                             | One immunosuppressed patient, on prednisolone then cyclosporine, developed clinical hepatitis. Cleared virus when immunosuppression stopped. Died from underlying condition |
| Japan, 2008   | [92] | 1                             | Retrospective study. Platelet transfusion with HEV 4. Recipient developed clinical acute hepatitis |
| Japan, 2007   | [93] | 1                             | Immunocompetent patient with T-cell lymphoma on chemotherapy. Chronic infection after HEV-contaminated red cell transfusion |
| France, 2007  | [94] | 1                             | 7-year-old immunosuppressed child, on chemotherapy. Acute post-transfusion hepatitis |
| UK, 2006      | [95] | 1 / 2                         | Two patients received HEV-contaminated blood products. Immunocompetent recipient did not develop HEV. Second recipient was immunosuppressed (lymphoma on chemotherapy) and developed acute post-transfusion hepatitis |
| Japan, 2004   | [96] | 1                             | Acute post-transfusion hepatitis following receipt of HEV-infected fresh frozen plasma |

In all the above studies, HEV was genotype 3 where sequencing data were available, unless otherwise stated.
There is particular concern about the use of plasmapheresis, which uses pooled plasma, often from thousands of donors. Current treatment methods appear not to remove or inactivate HEV from pooled plasma, and plasmapheresis has been shown to transmit HEV to transplant recipients in France [87].

**Should we screen blood donors for HEV?**

There is currently a very lively debate about whether blood donors should be screened for HEV [98]. This has been brought to a head by the recent Lancet paper by Hewitt and colleagues discussed above [57]. The authors concluded that: ‘on a clinical basis alone, the resulting minimal burden of disease does not signal a pressing need for donation screening at this time’. This statement is however reminiscent of the initial reluctance to consider screening for HCV over 20 years ago [98]. Protagonists of screening would argue that, in common with any retrospective analysis, data collection in the Hewitt study was far from complete and there were no follow-up data at all on 17 HEV-infected recipients. Also, our understanding of the places HEV ‘hides’ is still developing and the clinical phenotype of hepatitis E is still emerging. Nucleic acid amplification testing will begin in Europe in 2015 of pooled plasma processed with solvent detergent [72]. The issue of safety of plasma-derived medicinal products is also under active review by the European Medicines Agency.

If blood donors should be screened for HEV, how should this be done? The answer to this is uncertain, as most viraemic donors have a normal ALT, and often have absent anti-HEV antibodies [72,75]. Nucleic acid amplification testing will probably be the technique of choice, but this remains to be determined.

**Conclusions**

Zoonotic HEV is a remarkably successful virus. It has several niches in animals, and appears in various ways in humans. It causes acute and chronic hepatitis. It causes a range of neurological injury. It has found its way into the blood supply. Like other successful RNA viruses, such as HIV and HCV, it has several members of the public have never heard of HEV. Should we knowingly expose them to this virus by blood transfusion? We think not. That would be like allowing the virus to win at the game of ‘hide and seek’. Zoonotically acquired HEV is, arguably, one of the most successful zoonotic viral infections in human history, and has required little assistance from us humans to achieve this.

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