Hepatitis E: The ‘New Kid on the Block’ or an Old Friend?

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Locally acquired zoonotic hepatitis E virus (HEV) has ‘arrived’ in developed countries [1, 2]. Of considerable concern, and eloquently and thoroughly described by Dreier and Juhl [3], HEV has found its way into the blood supply. The numbers of viraemic donors are worryingly high in a number of developed countries, particularly in Germany.

HEV is considered by many as the ‘new kid on the block’. Is this true? A few years ago, when my colleagues and I described locally acquired hepatitis E as an ‘emerging infection’ in developed countries, we almost certainly made an error [1]. The evidence suggests that HEV is an ancient virus, and biological time-clock studies show that HEV diverged into its four genotypes several hundred years ago [4]. It would be more accurate to describe locally acquired hepatitis E in developed countries as a disease that is ‘emerging in human consciousness’. How long has HEV been in the blood supply in developed countries such as Germany? No one knows for sure (yet). My best guess is that HEV has been in the blood supply ever since the advent of blood transfusion.

I have been studying locally acquired, zoonotic HEV for over 10 years. Although I am not a virologist, HEV strikes me as an unusual virus, for two reasons. Firstly, although exposure to zoonotic HEV occurs in all age groups, including children, it appears to cause clinically evident hepatitis mainly in middle aged/elderly males [2]. The reason for this observation is not known, but I cannot think of another virus that behaves in such a manner. Nor can any of the very eminent virologists that I have talked to about this issue over the years. The second reason that I think that HEV is unusual is that it is a virus which likes to hide from human scrutiny. HEV has been playing ‘hide and seek’ with us humans for centuries. It has, until very recently, been winning this ‘game’. I realize that virologists would never ever think about a virus in such human terms. However, I am not a virologist, I am a clinical gastroenterologist. I would ask forbearance of virologist readers, and allow me to explain what I mean.

HEV ‘Hides’ in the History Books

HEV was discovered 30 years ago. ‘Look-back’ studies showed that HEV was responsible for large outbreaks of hepatitis in developing nations, such as the one in Delhi, India, in 1952/1953 involving over 29,000 cases with 100 deaths in pregnant women [5]. Deaths in pregnant females appears to be a unique ‘signature’ of waterborne HEV genotypes 1 and 2. Earlier historical descriptions of outbreaks of jaundice and deaths in pregnant women suggest that in the 19th and early 20th centuries hepatitis E was present in Germany, France, Italy and the Balkans [6]. The first such description of outbreaks of jaundice with associated deaths in pregnant females was in Lüdenscheid, Germany, in 1794 [7]. This outbreak included 70 cases of jaundice, including three pregnant women, two of whom died. It is thus probable that HEV has been causing human disease in Germany for over 200 years.

By the middle of the 20th century, outbreaks of jaundice associated with deaths in pregnant women stopped occurring in Europe and started to appear in developing countries in Africa and Asia. One explanation for these observations is that improvement in water sanitation in Europe asserted negative ecological pressure on HEV genotypes 1 and 2, which migrated south and east, leaving genotype 3 in its primary host, the pig [6].

HEV ‘Hides’ in Animals and the Environment

HEV was discovered in pigs only as recently as 1997, by X.J. Meng and colleagues in the USA [8]. How long HEV has been ‘hiding’ in pigs is not certain, but possibly for hundreds of years. Pigs (farmed animals and wild boar) are considered the primary host, but HEV from deer and rabbits have also been implicated in human disease. Zoonotic HEV (genotypes 3 and 4) have been found in pigs world-wide, and in porcine

products in the human food chain. Consumption of HEV-infected pork is one documented route of human infection, but there may be others [2].

Pigs infected with HEV have no symptoms and can excrete huge quantities of virus in their stool. HEV genotype 3 has been found in pig slurry lagoons, rivers, the sea, shellfish and soft fruits [9]. All the above are potential sources of human infection, and other 'hiding places' of HEV are being actively sought. For example, in our large cohort of well-documented cases of locally acquired hepatitis E in Cornwall, UK, approximately 50% of cases live within 2 km of the coast [10]. The cause of such geographical coastal clustering is unknown, but one explanation is that some of these cases may be due to recreational use of contaminated beach areas and coastal waters.

HEV 'Hides' in Populations

As Dreier and Juhl [3] describe, HEV genotype 3 is found in a surprisingly large number of blood donors in several developed countries, confirming that there are relatively large amounts of circulating virus in the human population. Another way of thinking about the amount of circulating virus in a population is by anti-HEV IgG seroprevalence. It is a crude epidemiological tool, depends on the sensitivity and specificity of the assays employed and is the subject of considerable debate.

Many early anti-HEV IgG seroprevalence studies in developed countries showed that 1–2% of blood donors were anti-HEV IgG-positive. This led us to the mistaken notion that HEV was not a big deal. For example, in a paper from 1993, Hans Zaaijer and colleagues [11] showed that the seroprevalence in blood donors from the Netherlands was 1.1%. The same group recently published data using a more sensitive assay on Dutch blood donors from 2011. The seroprevalence was 27%, 1 in 2,671 blood donations were found to contain HEV RNA, and the incidence of infection was 1.1% [12]. This set of observations from the Netherlands can only have two possible explanations: i) there has been an enormous increase in HEV infection in the Netherlands between 1993 and 2011, or ii) the assay used in the 1993 study was hopelessly insensitive. In Germany, a recent comparison of 3 anti-HEV IgG assays produced very divergent seroprevalence estimates: 4.5%, 18% and 29.5% [13]. Given the number of German blood donors who are viraemic at the time of donation (up to 1 in 1,200 [14]) the higher seroprevalence figures appear to have more 'face validity'.

Although there is evidence [15] to suggest that the Chinese assay which produces the highest seroprevalence estimates has high sensitivity (98%), the specificity of this assay to detect distant infection has not been properly documented (nor has it for any of the currently employed assays). In fact, it is quite impossible to confirm IgG specificity to distant infection with 100% certainty, and concordance studies/western blotting

have been unhelpful. However, there is circumstantial evidence which suggests that the Chinese assay may have acceptable specificity. In Southwest France this assay produces a seroprevalence estimate of 52% in blood donors [16]. In children aged 2–4 years from the same area using the same assay, the seroprevalence was 2% [16]. The latter result is not compatible with an assay that lacks specificity, but the high seroprevalence in blood donors is compatible with the very high incidence of HEV infection in this area (3.2%) documented using molecular tools. In addition the Chinese assay has produced much lower estimates of seroprevalence in some adult populations, including 4.7% in Scottish blood donors [17] and 2.2% in Fiji (Halliday JS et al: Seroprevalence of hepatitis E virus in three South Pacific countries. Submitted for publication).

In summary, the early seroprevalence studies were almost certainly flawed due to lack of assay sensitivity. This led us to adopt the 'received wisdom' that HEV was rare in developed countries, and only occasionally seen in travelers returning from endemic areas in Asia and Africa. However, zoonotic HEV was with us all the time, hiding in the population, unseen by blinkered human eyes.

HEV 'Hides' in Patients

Perhaps the most interesting, and certainly the most clinically relevant, place zoonotic HEV 'hides' in developed countries is within our patients. Our understanding of the clinical phenotype of hepatitis E infection has changed completely in the last 5 years, and continues to rapidly evolve.

The majority of humans exposed to HEV genotypes 3 and 4 are asymptomatic (fig. 1), and only a small minority has clinically symptomatic acute infection. The clinical phenotype of patients with acute symptomatic hepatitis E resembles that seen in any other form of viral hepatitis, but there are several important differences (see below). There is a very high mortality in patients with pre-existing chronic liver disease [1, 2, 18]. Such patients are not easy to diagnose and often present with a picture very similar to that of decompensated chronic liver disease caused by alcoholic hepatitis. Often the only clue in these cases is a brief serum transaminitis (ALT > 1,000 U/l). The transaminitis is very transient and easily, and possibly quite frequently, overlooked [18].

Acute hepatitis E may be mistaken for drug-induced hepatitis. This is an easy error to make as both poly-pharmacy and drug-induced liver injury are common in the elderly, as is hepatitis E infection. Some years ago, we took a systematic look at patients with 'criterion-referenced' drug-induced liver injury and found that in 13% of cases we had made a diagnostic error, as on retrospective testing they had HEV genotype 3 infection [19]. These observations suggest that the diagnosis drug-induced liver injury is not secure without first excluding hepatitis E as a possible cause, particularly in patients with predominant transaminitis.

The finding that HEV can cause chronic infection in the immunosuppressed, was a paradigm shift [20, 21]. Almost overnight, HEV was on the ‘radar’ of transplant physicians worldwide, as 60% of immunosuppressed transplant recipients fail to clear HEV on exposure. Chronic infection occurs in all types of transplant recipient, adults and children, and leads to rapidly progressive cirrhosis (10% in 2 years) if untreated [2]. However, it is not straightforward to make a diagnosis. Patients have no symptoms, and the ALT is only very mildly elevated (100–300). The prevalence of chronic HEV infection is 1–2% in the European transplant population, but it is much higher in Toulouse, France, for reasons that are unknown [2]. How long has zoonotic HEV been in the transplant population? This is unknown, but probably since transplantation was introduced into clinical practice in the 1960s.

HEV ‘Hides’ with the Neurologist

There have been an increasing number of case reports and small case series describing HEV-associated neurological injury. The spectrum of reported neurological injury is wide and includes Bell’s palsy, encephalitis, peripheral neuropathy, neuralgic amyotrophy and Guillain-Barré syndrome [22]. HEV-associated neurological injury occurs in both acute and chronic HEV infection, and in some cases HEV RNA has been found in the cerebrospinal fluid. In nearly every case the neurological symptoms and signs dominate the clinical picture: patients are usually not jaundiced, the ALT is only modestly elevated (100–500 U/l), and occasionally the liver function tests are normal. The pathogenic mechanisms are uncertain.

A very recent case control study of 201 patients with Guillain-Barré syndrome from the Netherlands [23] has confirmed that a minority of patients have evidence of HEV infection at the start of their neurological illness. In addition another Anglo/Dutch cohort study [24] of 47 patients with neuralgic amyotrophy showed that a significant minority had evidence of HEV infection at the onset of neurological symptoms. In both these studies (which are shortly to be published in full as back-to-back papers in *Neurology*, together with a podcast, and well worth a view) none of the patients were jaundiced, and the ALT was only modestly elevated and sometimes normal. This led the lead neurologist to ask me the following question:

‘Harry, is it possible that this virus has been misnamed? All these patients have significant neurological illness, but do not have much of a hepatitis!’

This is an interesting question.

Conclusions

Should we screen blood donors for HEV? In my view the answer to this question is yes. It is inevitable. It is not a question of ‘if’ but ‘when’. Naturally, full and rigorous risk assess-

Fig. 1. Most cases of zoonotic, locally acquired, hepatitis E in developed countries are asymptomatic. Only a small minority has clinically evident hepatitis. The grey areas represent emerging clinical phenotypes of HEV infection, including a range of neurological syndromes.

ments need to be performed. When such risk assessments are done, it is vitally important that careful attention is played to the emerging clinical phenotypes associated with HEV, including neurological syndromes.

HEV is the commonest cause of hepatitis worldwide [2]. Zoonotic HEV is the commonest cause of acute hepatitis in the UK [25], and probably most other developed countries too. It seems counter-intuitive to test patients presenting with acute hepatitis for other less common causes of acute hepatitis (HAV, HBV, HCV), and if these tests are negative, then consider testing for HEV. This diagnostic testing algorithm is common practice throughout Europe (including the UK and Germany), and reflects outdated, discredited ‘received wisdom’. It makes much more sense to first test cases of acute hepatitis for HEV, and if this test is negative, then test for the other less common causes of acute viral hepatitis.

We are making progress with the game of ‘hide and seek’ with zoonotic HEV. We have not yet won the ‘game’, and keeping a high index of suspicion and a low threshold for testing are two key strategies to ensure success.

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