Hepatitis E - A global review and its importance for health care practitioners and travellers from the UK

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Introduction

Hepatitis E is a growing health problem worldwide. This paper describes its first recognition, characteristics, where it might be found, then presentation, diagnosis and treatment. Infection prevention and progress towards a vaccine are outlined. Relevance of hepatitis E to a doctor working in a non-endemic country such as the UK is discussed.

History

Hepatitis E is the most recently discovered form of non-A - non-B viral hepatitis. it was first classified as a distinct disease during an outbreak of hepatitis in Kashmir, India 1978-82. it was initially thought simply to be hepatitis A, but the large numbers of affected patients who should have had at least some level of immunity to hepatitis A suggested that, something else was causing the outbreak. Virus-like particles were found when electron microscopy was performed on the faeces of a patient. This virus was later named 'hepatitis E virus'[1]

The earliest retrospectively confirmed outbreak of Hepatitis E occurred in New Delhi, India 1955-56. Stored serum samples were tested from what, at the time, was known only as an epidemic of water borne hepatitis.[2]

The Virus and its Epidemiology

Hepatitis E is a non-enveloped single stranded RNA virus. Four genotypes are recognised[2]:

Genotype	Location
Type one	Sub-tropical countries in Africa and Asia
Type two	Mexico, Nigeria, Chad
Type three	Worldwide incl. Asia, Europe, Oceania, North and South America
Type four	Asia

Hepatitis E is found worldwide, but the rates in developed countries are so low that 4 infected passengers arriving in the UK off a cruise ship in 2008 was news-worthy.[3] Other countries, particularly in Asia and Africa, suffer occasional outbreaks that can affect large numbers, interspersed with sporadic small outbreaks and occasional single cases

There is an incubation period of 2 - 9 weeks (average around 6 weeks),[4] followed by onset of clinical symptoms similar to other acute viral hepatitis infections lasting up to 4 weeks. Hepatitis E carries a

very low mortality rate for an average, otherwise healthy, member of a given population. However, especially during pregnancy, it can carry a high mortality risk. Hepatitis E has four main methods of transmission. By far the commonest is via water, where the virus is spread via a faecal-oral route and is thus particularly common in locations where sanitation is poor. This makes it a risk in the less economically developed parts of the world, as well as following natural disasters such as earthquakes, which can disrupt local sanitation systems. Flooding can also be very dangerous when contaminated water mixes with water that is normally suitable for drinking.[2]

Up to 70% of sporadic cases of acute viral hepatitis in India can be found to be due to hepatitis E if serological tests are performed. it is difficult to get accurate prevalence information, as the countries in which Hepatitis E is endemic, tend to have fewer healthcare resources and so a self-limiting infection is unlikely to result in serological testing and thus be recorded as hepatitis A or non-A, non-B.

Hepatitis E is additionally thought to be a zoonosis. Domestic swine have been linked with transmission of genotypes 3 and 4. This is believed to be the main source of hepatitis E in non-endemic countries, apart from that acquired during foreign travel. The virus affects humans when the animal carrying the virus is used as a food source.[2]

A third method of hepatitis E spread is by transplantation of an infected liver - typically in also the main method by which chronic hepatitis E is spread as the acute infection is usually self-limiting so the patient usually either recovers or occasionally dies from fulminant hepatic failure.[5] Materno-fetal transmission of hepatitis E from mother to child[5] is essentially unique to the endemic regions.

Presentation

Hepatitis E has various presenting symptoms, thus has the potential to be mistaken for other forms of hepatitis making it difficult to diagnose on clinical grounds alone. it often has quite mild symptoms but can be severe. The symptoms usually associated with hepatitis E include jaundice, fatigue, abdominal pain, hepatomegaly, nausea or vomiting, diarrhoea, fever and anorexia.[5] its mortality rate is 0·4-4·0%, usually due to fulminant hepatic failure which is frequently fatal.[2]

Diagnosis

Hepatitis E may be suspected from the history, particularly when the patient lives in or has travelled to a region where hepatitis E is endemic. There is no way of differentiating hepatitis E from other forms of viral hepatitis solely from clinical examination.

if hepatitis E is a possibility the next step is to test for hepatitis E antibodies if these tests are available -specifically, igG anti-hepatitis E virus antibodies and/or igM anti-hepatitis E virus antibodies. The test for igG antibodies in particular has high levels of both sensitivity and specificity, compared to the igM which has high specificity but poor sensitivity.[6]

Antibody	Sensitivity	Specificity
IgG	87%	92%
IgM	53%	99%

Anti-hepatitis E virus antibodies can be detected by performing a PCR test on the blood sample. However, this is unlikely to be cost effective for a sin-gle patient.[6] Other blood tests can be performed to exclude other viral causes of hepatitis - including Hepatitis A, B, C, cytomegalovirus and Epstein Barr infection.

Leptospirosis and amoebiasis may have to be considered.

Standard liver function tests and coagulation tests should also be performed, particularly if the patient has become jaundiced, to assess the severity and fol-low the course of the illness. imaging studies do not provide any useful diagnostic information, except as a method of ruling out other potential diagnoses.

Treatment

There is currently no specific curative treatment for hepatitis E, with most studies focused on prevention rather than cure. Assuming the patient does not appear to be developing fulminant hepatic failure, the patient should be treated supportively.[4] with particular attention to adequate fluid intake orally or intravenously. Care should also be taken to avoid drugs that are metabolised by the liver especially if there are signs of liver failure.

if liver failure develops they will require intensive care. it is possible at this stage for a patient to recover spontaneously, but unlikely, so early transfer to a transplant unit must be considered.

However countries with high rates of hepatitis E, while correspondingly have the majority of cases that progress to liver failure, typically have fewer medical resources making intensive care difficult and transplants difficult or impossible.

PreventionThere are three different levels of potential hepatitis E prevention: individual, national and international. At an individual level, in countries where hepatitis E is endemic, preventing infection with hepatitis E is the same as preventing infection with any other water borne infection - particularly the very simple advice - "Don't drink contaminated or untreated water!" should be followed - this

Table 1

COUNTRY	Population in 1000	Total Deaths	Total WSH-Related	% of total deaths
Bangladesh	143809	1106.8	109.9	9.9
Bhutan	2190	21.0	1.9	9.2
DPR Korea	22541	204.4	7.1	3.5
India	1049550	10378.5	782.0	7.5
Indonesia	217131	1626.1	57.3	3.5
Maldives	309	2.1	0.1	6.0
Myanmar	48852	519.9	44.0	8.5
Nepal	24609	233.3	24.7	10.6
Sri Lanka	18910	145.5	2.7	1.9
Thailand	62193	419.1	13.5	3.2

Table 1 is part of a larger table taken from source 8

includes ice cubes and drinks made using water such as cordials. Raw or unpeeled fruit or vegetables may have been washed in the contaminated water. Any possibly suspect foods should be well cooked and be hot when consumed, particularly fish that may have been living in contaminated local water.[7]At a national level the key issue in hepatitis E prevention is provision of safe public drinking water and good local sanitation. This is especially important in areas suffering regular monsoon rains and/or regular flooding because this makes it significantly more likely that local water supplies will become contaminated. Problems can also arise due to damaged pipes supplying drinking water running alongside dam-aged pipes carrying sewage.[2]The chart below details the numbers of deaths in a number of Asian countries due to contaminated water in 2008. Whilst the information is not specific to hepatitis E, it does show how useful improvements in sanitation would be from a general public health point of view, as well as being useful in the prevention of hepatitis E.[8]

At an international level, reducing the rates of hepatitis E could be helped by the production of a vaccine -discussed later. The most important point about the vaccine is that currently there are no licensed vaccines available although there are currently sever-al promising trials.

Risk Factors

Certain conditions greatly increase the risk of a severe viral hepatitis with increased risk of fulminant hepatic failure and death. The most common is pregnancy: the mortality rate of hepatitis E in pregnant patients is 25-33%. The mechanism of this is unknown but high levels of steroid hormones present in pregnant women may cause the liver to be more vulnerable to infection.[5,9]

Hepatitis E mortality rises with patient age: the cause of this is unclear.

Vaccine

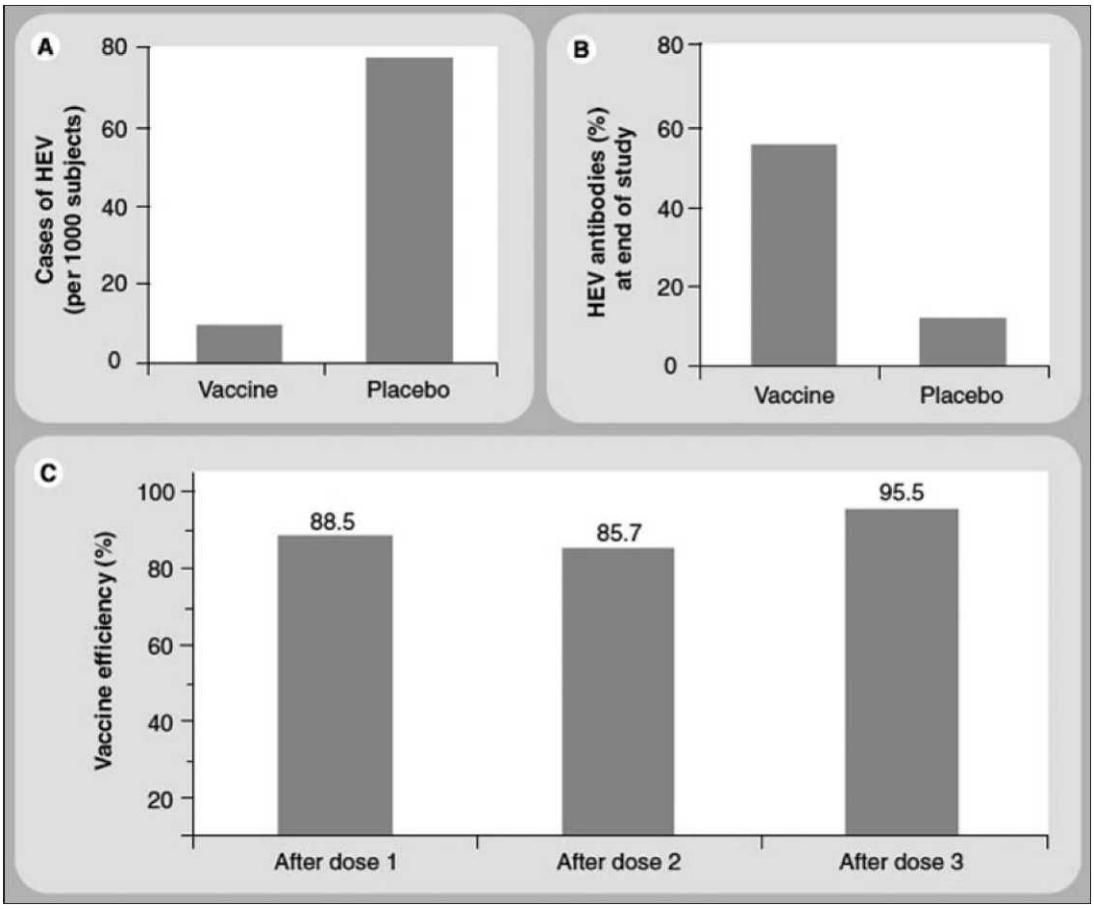
There are currently no vaccines licensed for use in preventing hepatitis E infection.

However, several have been tested and one has recently passed through phase 2 clinical trials with promising results. in 2007, a clinical trial in Nepal recruited 2000 members of the Nepalese army and administered the vaccine at zero, one and six months. The tables show the results.[10]

Table A shows that there is a higher incidence of hepatitis E infection among soldiers given the placebo than among those who were given the vaccine. Table B shows that vaccinated soldiers were more likely to have circulating antibodies against hepatitis E virus than those who were given the placebo, although the difference was not as marked. The final table shows that the incidence of hepatitis E was significantly lower in the vaccinated soldiers than in soldiers given the placebo.

Despite this success in clinical trials, there have been no studies looking at the length of immunity provided by this vaccine, and current indications suggest that the immunity may be transient, although how transient is unknown. This means that the vaccine, while suitable for travellers and helpful for army units, may not in its current form be useful for population wide immunisation. There is also some doubt as to how effective the vaccine may be against hepatitis E spread via animal reservoir as opposed to water borne hepatitis E.

Table 2



Graphs based on information from source 10

in December 2011 China's State Food and Drug Administration (SFDA) approved a vaccine for use in the prevention of hepatitis E infection. in October 2012 provision of the vaccine to the public began.[11] The vaccine was proven to be both effective and well tolerated in a trial performed in 2009/10. The trial was performed over 19 months with the primary end-point of patient follow-up being 12 months from the 31st day following the third and final dose of the vaccine. The trial was a double blind, placebo-con-trolled trial performed across as wide a cross section of the population as possible accounting for both age and gender.[12]

Despite the availability of this vaccine in China, there is still no vaccine licensed for use in Europe or the USA. This is likely to be due, at least in part, to the very low levels of hepatitis E within these areas and the self-limiting nature of the disease so development of a vaccine is not seen as a priority for funding.

How important is Hepatitis E for the UK Doctor?

Firstly, studies in the USA have suggested that there may be a seroprevalence of 1-20% of anti-hepatitis E virus antibodies within the population of developed countries.[5] This is a source of contention, particularly with the wide variance in the suggested seroprevalence. One possible cause of this variance is that different tests will have been used in different places and by different studies leading to differing results.

There is the possibility that rates of hepatitis E are higher than previously realised simply due to it being misdiagnosed as hepatitis A or as non-A, non-B hepatitis and since the virus is self-limiting the patient goes home well but misdiagnosed. Another possibility is that there are significant levels of subclinical hepatitis E which allow the introduction of anti-hepatitis E virus antibodies into the population.

Another reason for UK doctors to be aware of hepatitis E is the gradual rise in non-travel related cases that have been appearing in the UK in the last decade. Again, it is possible they have been occurring for longer than previously realised and have not been recognised or perhaps we are testing for the infection more frequently in jaundiced patients.

Large numbers of UK citizens travel to regions where hepatitis E is endemic for holidays, or as volunteers or aid workers. Since the incubation time for the virus can extend to nine weeks, it is not difficult for someone to contract hepatitis E whilst away and then return to the UK before showing any clinical signs. in these cases it is important for the doctor to enquire if patients have visited these regions should they develop hepatitis symptoms.

in 2008 a ship returned to the UK from an 11 week round the world cruise. 4 passengers were ill from what was found to be hepatitis E, as well as 33 others with antibodies indicative of recent infection. in this case the source was thought to have come from fish picked up whilst the ship was docked in an endemic country during the trip.[3]

Conclusion

Hepatitis E is a recently discovered virus with a significant prevalence in the developing world. With the high likelihood that symptoms will remain mild and the self-limiting nature of the viral hepatitis it may be viewed as a relatively minor problem. However, the large number of cases in endemic areas and the time needed to recover, regardless of the mild-ness of symptoms, makes hepatitis E a major problem.

Additionally, increasing numbers of patients affected by the virus will lead inevitably to an increased number of patients suffering the more severe symptoms of the infection, increased numbers developing chronic hepatitis and increased mortality from the disease. The large increase in risk associated with pregnancy is also a concern.

The relevance of hepatitis E to doctors across the developed world has been shown with studies suggesting a far higher seroprevalence of anti-hepatitis E virus antibodies in the populations of the

developed world than would be expected, and all doctors should be aware of the risks associated with citizens of developed countries travelling to those regions endemic for hepatitis E.

On a more positive front, there is good progress being made with a potential vaccine that is showing itself to be very effective in the short term, although longer term studies will need to be undertaken to con-firm the length of immunity conferred by the vaccine and get the vaccine to the point of being licenced. Over the next few years a much more effective response to the problems posed by Hepatitis E may be available.

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