

Chapter 4: Hepatitis E - Epidemiology, transmission and natural history

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Introduction

Like hepatitis A, the hepatitis E virus is a non-enveloped single stranded RNA virus of an icosahedral shape, measuring 27-34 nm in diameter. It is the sole member of the genus *Hepevirus* in the family of *Hepeviridae* (Emerson 2004). Its existence was hypothesised when a retrospective analysis of clinical samples collected during hepatitis outbreaks in India in 1955 with newly developed essays for hepatitis A and B showed a high prevalence of close to 100% for anti-HAV IgG but no sign of acute hepatitis A or B. Thus the conclusion was that there must be another infectious agent for enterically transmitted non-A non-B hepatitis (ET-NANB) (Khuroo 1980; Wong 1980). HEV was first visualised in 1983. It was transmitted to a human volunteer in Russia and to cynomolgus monkeys, causing acute hepatitis in both, and thus establishing its etiologic role in ET-NANB hepatitis (Balayan 1983).

Three large open reading frames (ORFs) of the positive-sense RNA of HEV have been described. While the largest ORF consisting of 1693 codons encodes for non-structural proteins responsible for the processing and replication of the virus, the other two ORFs (660 and 123 codons, respectively) encode for structural polypeptides (Koonin 1992). Four genotypes and multiple subtypes of HEV have been identified by phylogenetic analysis of stored HEV sequences.

Genotype 1 HEV is the main cause of hepatitis E in developing regions of Asia, Africa, and South America. In patients in Mexico, Chad, and Nigeria genotype 2 has been identified (Buisson 2000; Cuyck-Gandre 1997; Tam 1991). Genotype 3 has been found in cases of autochthonous hepatitis E in many developed regions (Banks 2004; Garkavenko 2001; Wibawa 2004) while genotype 4 has been found in industrialized regions of Asia (Lu 2006; Wang 2002). Genotypes 1 and 2 HEV appear to be confined to humans only, genotype 3 and 4 have been found in swine and wild animals (Lu 2006). Only one serotype of HEV is known.

Epidemiology and transmission

The characteristics of hepatitis E epidemiology are similar to those of the hepatitis A virus. Areas with endemic infections and high incidence are in Asia, Africa, Central America and the Middle East (Belabbes 1985; Gupta 1957; Arankalle 1988; Tsega 1991; Velazquez 1990). Here the predominant mode of infection is faecal-oral via contaminated water (Belabbes 1985; Naik 1992). Large outbreaks of HEV have been described. The largest documented incident was in China between 1986 and 1988 involving over 100,000 individuals (Zhuang 1992). Parenteral transmission by blood transfusion seems to occur especially in areas where HEV occurs endemically (Mat-subayashi 2004; Khuroo 2004).

In industrialised countries the disease occurs sporadically. Most infections are diagnosed in individuals who travel to countries where HEV is endemic. It has however

been questioned if all cases are imported, for example when high rates of hepatitis E antibodies were found in drug users in Denmark and Sweden (Sylvan 1998; Christensen 2002). This may indicate parenteral transmission by needle sharing within the group. Furthermore, HEV was found in sewage samples collected in France, Spain and the United States (Buti 2003). There is evidence of autochthonous HEV in these areas. In a retrospective analysis of 28 patients in the United Kingdom who were previously diagnosed with drug-induced liver injury 21% actually were actually infected with HEV (Dalton 2007). One could conclude from these findings that the incidence of HEV in industrialised countries may currently be underestimated and that HEV infection may well be underdiagnosed.

Zoonotic transmission needs also to be mentioned. People with occupational contact with swine in the United States (veterinarians and farmers) show a high seroprevalence of anti-HEV antibodies (Meng 2002; Karetnyi 1999). Rodents may also function as a reservoir in some regions (He 2006). Two case studies from Japan demonstrated transmission by undercooked wild boar and deer meat to humans (Tei 2003; Li 2005). To this day the extent of endemic or zoonotic transmission is not fully understood.

Vertical transmission of HEV infection from mother to child has been identified. In one study of eight pregnant women with acute hepatitis E, five blood specimens collected from their babies at birth tested positive for HEV RNA (Khuroo 1995).

Clinical features

The disease may range in severity from sub-clinical to fulminant liver failure. Pregnant women are at especially high risk with a death rate approaching 20%. Overall fulminant fatal hepatitis E occurs in 0.5-3% (Herrera 1993).

After an incubation period of 15 to 60 days (Khuroo 1980; Bayalan 1983) the infected patient develops symptoms and clinical signs that resemble those seen with other forms of acute viral hepatitis. The most prominent feature is jaundice accompanied by general symptoms such as malaise, anorexia and fever, as well as abdominal pain, nausea, vomiting and hepatomegaly. Other clinical symptoms are diarrhoea, pruritus, arthralgia and rash. In biochemical analyses elevated serum concentrations of bilirubin, alanine aminotransferase and aspartate aminotransferase can be seen. Laboratory and clinical symptoms usually resolve within a few weeks to two months. Compared to hepatitis A the disease appears to be more severe with protracted coagulopathy and cholestasis in more than half of patients (Chau 2006).

A study from Japan compared the clinical features of patients infected with genotypes 3 and 4 and saw that genotype 4 tends to have more severe clinical manifestations than genotype 3 (Ohnishi 2006). It was observed that genotype 4 infected individuals had significantly higher alanine aminotransferase peak levels (median 3430 IU/L vs. 1052 IU/L), a lower trough prothrombin time (61 vs. 84%) and that the median time in hospital was longer (26.5 vs. 18 days).

Liver histology in a study of eleven patients with sporadic acute hepatitis E showed acute hepatic lesions in all cases. Nine samples displayed marked necro-inflammatory activity and in five, confluent necrosis was present. Siderosis and cholestasis were diagnosed in eleven and nine patients, respectively (Peron 2007).

The sero-epidemiology of hepatitis E suggests that individuals previously infected with HEV are protected during epidemics of the disease, indicating that immunity to HEV is induced and prevents reinfection (Bryan 1994).

Hepatitis E is widely accepted to be self-limiting and not to progress to chronic disease. However, recent reports describe patients who underwent organ transplant and subsequent immunosuppressive therapy and who may develop chronic HEV infection. In a group of 14 organ recipients (liver, kidney, pancreas) that were diagnosed with acute HEV, chronic hepatitis developed in 8 patients as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis (Kamar 2008). Two cases of chronic HEV infection in liver transplant recipients leading to cirrhosis and graft-failure have been reported (Haagsma 2008). The same group found a prevalence of HEV infection acquired after liver transplantation in 274 patients of only 1% (Haagsma 2009). It remains to be determined if there is a substantial risk for immunosuppressed patients of developing chronic HEV infection.

Diagnosis

Diagnosis of acute hepatitis E is based upon the detection of antibodies to HEV or detection of HEV RNA in serum or faeces. HEV RNA may be found very early in faeces and serum. It usually becomes undetectable within one to six weeks after the onset of symptoms (Takahashi 2005). Anti-HEV IgM antibodies are also present early in infection and remain positive for months. Formation of anti-HEV IgG can be detectable as early as in the second week of clinical symptoms.

Combined testing for anti-HEV IgG and either anti-HEV IgA or HEV RNA may be helpful in areas of higher HEV prevalence to distinguish ongoing from remote infection (Takahashi 2005), as anti-HEV IgM (or anti-HEV IgA) alone may be present in individuals with previous HEV contact. Also IgM rheumatoid factor may cause false positive results.

Pregnancy

Fulminant hepatic failure occurs more frequently in pregnant women, resulting in a remarkably high mortality rate of 15 to 25%, primarily in women in the third trimester (Khu-roo 1981). The foetal and obstetric outcomes of pregnant women with jaundice and acute viral hepatitis E appear to be worse compared to hepatitis due to other causes (Patra 2007). In 220 consecutive pregnant women with icteric acute hepatitis in a hospital in New Delhi fulminant hepatic failure was more common and maternal mortality was higher (relative risk 2.7 and 6.0, respectively) in HEV-infected women than in those with other aetiologies. The relative risks for obstetric complications were: 4.1 for antepartum haemorrhage, 1.9 for intrauterine foetal death, 1.2 for preterm delivery, and 1.8 for stillbirth.

Treatment

Specific treatment is not available for hepatitis E infection and only monitoring is possible. As in most cases the infection is self-limiting and is followed by complete recovery without chronic sequelae, and no specific interventions are required. Patients with hepatic failure should be transferred to a centre capable of performing liver transplants.

Prevention

In areas with endemic HEV infection food and water sanitation is warranted especially for individuals that are immunosuppressed. It has to be kept in mind that at least some of the HEV infections in industrialized countries are autochthonous infections. These are not associated with travelling to high incidence countries but may be due to zoonotic transmission (Wichmann 2008). A vaccine based on ORF2 has been developed and successfully tested in a phase II trial in Nepal (Shrestha 2007). Another HEV vaccine based on the 50 kD recombinant capsid protein went through Phase III clinical trials at the Xiamen University in China (Feng-Cai 2009). To our knowledge the data of this trial has not been published yet. This topic is discussed in more detail in Chapter 7.

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