Hepatitis E: Review of a disease endemic in Pakistan
F. Shahzad, M. Atiq, S. Ejaz (Department of Medical Students, The Aga Khan University, Karachi.)
S. Hameed (Department of Medicine, The Aga Khan University, Karachi.)

Introduction

The primary hepatotrophic viruses (hepatitis A, B, C, D and E virus) are the most common cause of acute liver disease\(^1\). In developing countries the majority of these cases are caused by the hepatitis E virus (HEV)\(^2,3\). Hepatitis E is enterically transmitted, causing a self-limiting disease similar to hepatitis A. It is endemic in most developing countries, where it causes major epidemics and sporadic cases.

Epidemics of hepatitis E are thought to have occurred in Europe and the United States in the 18th and 19th centuries\(^4\). However, HEV was recognized as a separate disease in the early eighties when sera of patients from epidemics of viral hepatitis in Delhi and Kashmir were found to lack serological markers of acute hepatitis A or B and it was referred to as enterically transmitted non-A, non-B hepatitis\(^5\). The proof of its existence came in 1983 when virus-like particles were detected by immune electron microscopy from the faeces of a person infected with enterically transmitted non-A, non-B hepatitis\(^6\).

The genome of HEV was cloned in 1990 and fully sequenced subsequently\(^7\).

The WHO recognizes Hepatitis E as a significant health problem in many developing nations. Pakistan is endemic for all types of hepatitis and hepatitis E occurs here in both sporadic and endemic forms. Documented epidemics have occurred in Sargodha (1987)\(^8\), Abbotabad (1988)\(^9\) and Islamabad (1993)\(^10\). Some recent studies have shown HEV to be the most common etiologic agent of sporadic hepatitis in Pakistan\(^2\).

Epidemiology

Hepatitis E virus is endemic in developing countries. Several outbreaks have been reported from South Asia\(^11\), Middle East\(^12\), northern Africa\(^13\), and Central Asia\(^14\). Outbreaks usually occur after rainy seasons, flooding and recession of floodwaters\(^15\). They have also been associated with poor hygiene\(^16\) and unsafe water supplies\(^11,16\). An epidemic of hepatitis E infecting 3,827 people occurred in Islamabad after a water treatment plant broke down\(^10\).

Young to middle aged individuals between 15 and 40 years of age have the highest attack rates\(^17\). Males and females have been shown to be equally susceptible in acquiring hepatitis E. However, some reports have shown a >3 times higher attack rate in males\(^15\). Attack rates during an epidemic vary from 1\% to 15\%\(^5,19,20\). The case fatality rate from the general population is from 0.5\% to 4\%\(^16-18\). Hepatitis E is especially severe in pregnancy. The attack rates in pregnant females have been reported from 17\% to 40\%\(^18,21\). Pregnant females in the second and third trimesters exhibit a case fatality rate of 20\%\(^15,16,22,23\). Frequency of abortions, stillbirths and neonatal deaths is also increased in pregnant women with hepatitis infection\(^19\). However, this appears to be true only in developing countries because reports from Europe and USA have shown that the course of viral hepatitis in pregnancy is in no way different from that in non-pregnant women\(^24-26\). Altered immune response, hormonal changes associated with pregnancy and malnutrition have been postulated as the possible factors responsible for the increased severity of the disease during pregnancy\(^27\). None of the reports however have been able to conclusively attribute the fulminant course of the disease to these factors.

Phylogeny

HEV is a RNA virus, provisionally classified in the family caliciviridae, genus calicivirus on the basis
of its structural and physicochemical properties. It bears a closer resemblance to rubella virus and plant fUroviruses in its genomic organization. It is a single standard positive sense RNA molecule approximately 7.5 kh in length. The genes of 15 isolates have been fully sequenced. The are classified in 5 genotypes: genotype-I (Asta-Africa), genotype-II (United States). genotype-III (Mexico), genotype-IV (Beijing, China) and genotype V (Europe). Genotype I is the most complex, having 2 sub-genotypes: African and Asian. The Asian sub-genotype comprises of 2 genetic clusters: South Asian and Central Asian. The South Asian cluster includes isolates from Burma, India, Pakistan and Nepal. The Central Asian cluster includes isolates from China, Pakistan, Kirghistan and Uzbckistan.

In Pakistan, two phylogenetically distinct variants have been identified. The Sargodha isolate (Sar-55) belonging to the central Asian clusters of genotype I was identified in a 1987 epidemic. Abbotabad isolate (Abb-2b) which was subsequently identified from an epidemic in 1998 has been placed in the South Asian clusters of genotype I. The two Pakistani isolates were recovered 18 months apart from cities only 3000 kilometers from each other, but because they are also so distinct they must have had separate origin. There are many examples of travelers importing HEV. The geography of South Asia does not provide a barrier to the movement of the HEV from east to west, whereas unfavorable geography renders travel from Central Asia to Pakistan less frequent. Thus speculated that Abb-2b represent HEV endemic in Pakistan while Sar-55 was an unusual introduction from China.

Transmission
HEV is transmitted almost exclusively by the fecal-oral route. Person to person transmission appears to be distinctly uncommon. Nosocomial spread of hepatitis E has been reported in a hospital in South Africa. Hepatitis E occurs in both epidemic and sporadic forms. Most epidemics of hepatitis E have occurred through consumption of fecally contaminated drinking water. Transmission of sporadic HEV infections is unclear. Water contamination, food, fomites and person to person transmission may be possible factors. cases fire large epidemics is still speculative. In a study conducted in India, Santosh et al. showed protracted viremia in 4 out of 26 patients with sporadic hepatitis E. In one of these patients the fecal sample continued to remain positive for virus extraction up to the 52th day of icterus. Such cases might act as a reservoir for hepatitis E virus and are responsible for contaminating the water sources. Detection of HEV antibodies in the sera of pigs, sheep, cattle and rodents in endemic areas raise a possibility of zoonosis for HEV. Consumption of water sources by such domestic animals could also contribute to persistence of disease in endemic areas. Vertical transmission of HEV infection from mother to infant is known to occur. In one stuth 6 out of 8 babies born to mothers with either acute uncomplicated hepatitis or fulminant hepatic failure in the third trimester of pregnancy were found to have evidence of HEV infection. There is no evidence of HEV transmission by sexual contact or blood transfusion.

Clinical Features
HEV has an incubation period of 2 to 10 weeks. The disease manifests in a variety of forms, viz, an asymptomatic infection, anicteric hepatitis, icteric hepatitis and fulminant hepatic failure. The majority of patients have an entirely asymptomatic infection without any clinical manifestations. Others have a milder clinical course with non-specific features resembling those of a viral illness (anicteric hepatitis). The exact proportion of asymptomatic infections and anicteric hepatitis is not known but they account for the majority of cases because most sero-positive people in HEV endemic areas do not recall having jaundice.

Acute icteric hepatitis is the most common clinically detectable form of disease. It occurs in two phases. The first, called the prodromal phase, is pre-icteric lasting a few days. It is characterized by flu-
like symptoms, anorexia, nausea, vomiting, diarrhea, fever, mild chills, abdominal pain, asthenia, arthralgia, aversion to smoking, a transient skin rash, clay coloured stools and dark tea coloured urine. The second, the icteric phase, lasts for 1-4 weeks. It is characterized by darkening of urine, lightening of stool colour and appearance of jaundice. Itching may also occur. With the onset of jaundice, the prodromal symptoms rapidly diminish. Physical examinations show icterus and mildly enlarged, soft and slightly tender liver and occasionally a soft palpable spleen. Laboratory indices include bilirubinuria, a variable degree of bilirubinemia (predominantly conjugated), markedly elevated transaminases and GGT and mildly elevated alkaline phosphatase activity. Aminotransferase levels may start increasing up to 10 days before the onset of symptoms, peak by the end of the first week and start coming down as the illness resolves, normalizing by 6 weeks. The magnitude of aminotransferase rise is not related to the severity of liver damage. The disease runs a self-limiting course, usually resolving in 1-4 weeks. Chronicity has not been shown to occur. However, a few patients develop cholestasis with a prolonged clinical course. The bilirubin and alkaline phosphatase levels in these patients remain elevated with normal transaminase levels. The condition resolves in 2-6 months. Fulminant hepatic failure develops in a small number of cases. However, this infection is an important cause of fulminant hepatitis in endemic areas. A study conducted in India showed that HEV was responsible for 62% adult and 40% of the pediatric cases of sporadic fulminant hepatic failure. Pregnant females are especially susceptible to developing a fulminant course of this infection. In a study in Pakistan, two-thirds of a group of pregnant women with fulminant hepatic failure had HEV infection.

Pathogenesis
Incubation period in humans after oral exposure is 2 to 10 weeks. Viral antigens can be detected in the stool samples beginning approximately 1 week before onset of illness and persist for 2 weeks afterwards. IgM anti HEV appears during early clinical illness and diminishes over 4-5 months. IgG anti-HEV appears a few days after appearance of IgM anti HEV and its titers remain high from 1 to 4.5 years after acute phase of the disease. The exact duration of persistence of anti HEV is not known. One study showed 47% of people to have anti HEV 14 years after acute HEV infection. Thus, IgM anti HEV is a marker of acute or recent HEV infection while IgG anti HEV indicates infection, not necessarily recent.

ALT is elevated in up to 98% of the patients. The onset of ALT elevation corresponds to the detection of anti HEV in serum and decreasing levels of HEV antigens in hepatocytes. This suggests that the liver injury may be largely immune mediated, also since the infiltrating lymphocytes in the liver have been found to have a cytotoxic/suppressor immunophenotype.

Diagnosis
The diagnosis of HEV infection utilizes clinical symptomatology (dark urine, light colored feces and scleral icterus) along with biochemical evidence of elevated ALT levels. HEV genome can also be detected in serum or stool samples using RT-PCR, which has recently been modified to increase the sensitivity and reproducibility. The most commonly used method is the detection of HEV antigens in serum via ELISA. Target antigens in these essays are the recombinant proteins that correspond to the open reading frame (ORF-2, ORF-3) of the genome.
disease rates in pre and post exposure prophylaxis studies\textsuperscript{49}. Experimental vaccines for HEV have been developed and their effectiveness is being investigated\textsuperscript{50}.

**Summary**

Hepatitis E is enterically transmitted causing a self-limiting illness similar to hepatitis A. However, unlike hepatitis A, immunity to hepatitis E is not life long, hepatitis E is a disease of developing nations with improper sewage disposal and unclean water supplies. It is thought to be the most common cause of acute sporadic hepatitis in Pakistan, where it has also caused major epidemics. Hepatitise causes a mild self-limiting illness with no long-term sequelae. However, it is especially severe in pregnant females in the second and third trimesters, in whom it results in a high mortality rate (up to 20\%) and an increased incidence of stillbirths. Diagnosis depends on clinical findings and elevated hepatic enzymes. Protection from this disease in endemic areas lies mainly in prevention, as the vaccine for hepatitis E is still in the experimental stage. Provision of clean drinking water, hand washing before eating and proper disposal of sewage has been shown to decrease the incidence of this disease.

**References**


49. Khuroo MS, Dar MY, Hepatitis E: Evidence for person to person transmission and inability of low dose serum globulin from an Indian source to prevent it. Indian J. Gastroentrol,. 1992:11:113-16.