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Hepatitis E- not so benign after all!

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Abstract

Outbreaks and sporadic cases of Hepatitis E virus (HEV) are well known. But, chronic disease leading to cirrhosis is increasingly recognized in immunocompetent and immunosuppressed individuals. Transmission is commonly by the feco-oral route; but zoonotic, vertical and transfusion related transmission is also documented. Most HEV infections are either asymptomatic or present as acute self-limited viral hepatitis with a prominent cholestatic phase. Fulminant hepatic failure is a dreaded complication in pregnancy, underlying liver disease and immuno-suppressed patients including organ transplant recipients. Several other systemic complications are reported infrequently. Co-infections with other hepatitis viruses, HIV, EBV, salmonella, leptospira, etc; worsen the outcomes. Co- morbidities like alcoholism, chronic liver disease, sickle cell disease, collagen–vascular diseases and malignancy also alter the clinical course. Ribavirin and mycophenolate are showing promise in treatment of prolonged HEV infections in by preventing cirrhosis; and in transplant recipients by improving outcomes. Routine screening for transfusion safety is an issue, when it comes to cost of health care. An effective vaccine has been licensed for use in China.

Keywords: Hepatitis E virus (HEV), Complications, chronicity, Vertical and transfusion related transmission, Ribavirin, Vaccine.

Jaundice is the disease that your friends diagnose.

William Osler

INTRODUCTION

Many clinicians believe that Hepatitis E virus (HEV) infection contracted feco-orally causes acute, self-limited, uncomplicated viral hepatitis in most instances except pregnancy, where outcomes may be poor. During December 2015 to February 2016, an outbreak with several fatalities was reported from Shimla and Solan (in Himachal Pradesh) which was investigated by both- the NCCD and NIV [1, 2]. These reports are not yet in the public domain.

OUR EXPERIENCE: Ours is a busy public hospital having an average daily OPD footfall of over 7000 patients, where only the very sick qualify for an admission. In-patient care is mainly provided to economically weaker sections of society, without health insurance. This forces a limitation on paid investigations for in-patients.

The first case this year was a doctor, who had traveled from Shimla during the outbreak of 2016. He deteriorated rapidly and was sent to a specialized centre since he met the criteria for an urgent liver transplant (bilirubin >30 mg/dl, prothrombin time 50 seconds, INR 4.5 and jaundice to encephalopathy time < 7 days). His mother was a willing donor. But during transplant work-up there was improvement and surgery was not needed. Between February to May this year, 11 admitted cases of acute hepatitis turned out to be IgM anti-HEV positive and attracted attention due to their complicated clinical course. All except the first case had not travelled during the previous 3 months. Two were female and 9 were male. One female case had gestational diabetes. Another male had type 2 diabetes mellitus. Most male cases consumed alcohol regularly.

All had a typical short prodrome followed by deep jaundice and different degrees of hepatic decompensation resulting in a range of clinical manifestations and laboratory abnormalities. Clinical complications in decreasing frequency were edema, ascites, bleeding (gastrointestinal and utero-vaginal), encephalopathy and acute abdomen (one pancreatitis and one intestinal obstruction- probably intussusception from abdominal lymphadenopathy). Biochemical abnormalities were hyperbilirubinemia (14 to 32 mg/dl), intense transaminitis (peak enzymes in 3000U to 6000U range), varying hypoalbuminemia and prolonged prothrombin time/INR. Different degrees of deranged KFTs were seen in

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over half these patients, though none required dialysis. Serum amylase and lipase were raised in the case of pancreatitis. Platelet counts were in the low normal range. Leucocytosis was noted in both cases of acute abdomen. All were negative for IgM anti-HAV, HBsAg, anti-HCV and HIV. IgM Dengue, Malarial antigen test and Widal test were negative wherever done. IgM Leptospirosis was negative in one case with significant renal dysfunction. Standard management protocols were followed within available resources. We had 2 deaths (one puerperal female patient and one established alcoholic), 2 transfers to higher centre and 4 cases had a prolonged clinical course beyond 2 months. This was just a pilot survey with a strong selection bias since only the very sick were admitted, and work-up was limited by financial constraints. Even so, it gave enough reason for in- depth study; and to consider further research, preferably multi-centric.

Epidemiology

An estimated 20 million HEV infections and 3.3 million acute cases occur annually worldwide with an estimated 56,600 deaths. The highest incidence of HEV infection is in the underdeveloped tropical countries, although it is also reported from developed regions outside the equatorial belt and is probably more widespread than generally believed. Outbreaks and sporadic cases are both reported. East and South Asia are most affected with frequent outbreaks in the rainy season in resource-limited settings with unsafe drinking water, poor sanitation and health services. Some outbreaks are reported in areas of conflict and humanitarian emergencies [3, 4, 5]. The Shimla outbreak occurred in freezing winter. Fecal contamination and insufficient dilution of the shrinking water reservoir was implicated [1, 2]. Hepatitis E occurring sporadically or as disease outbreaks has been identified in at least 63 countries, of which about half have reported large outbreaks. There are also countries where serologic evidence in sufficient numbers, suggests endemicity [3, 5, 6]. In the largest reported outbreak, over 100,000 individuals were afflicted in the Xinjiang region of China between 1986 and 1988 [7].

Infection with this virus was first documented in 1955 during an outbreak in New Delhi [8], yet the burden of viral hepatitis in India is not well documented. National Integrated Disease Surveillance Programme (IDSP) conducted surveillance in 2011–2013 to report a total of 804,782 hepatitis cases and 291 outbreaks from 23 Indian States. Two-thirds of outbreaks were in rural areas of which 48% were caused by HEV and 12% by HAV and HEV co- infection [9]. No national figures are available after this.

HEV is an icosahedral, non-enveloped single stranded RNA virus of the Hepeviradae family. All HEV isolates belong to a single serotype, despite having five genotypes; of which four are human pathogens. Genotypes 1 and 2 are more virulent and cause outbreaks, while genotypes 3 and 4 are attenuated and account for subclinical infections. Genotype C is implicated in chronic HEV and infection in transplant recipients. Animal reservoirs like pigs, smaller mammals and shellfish contribute to the perpetuation of this virus. Most transmission occurs through the fecal-oral route but food-borne transmission from infected animals; transfusion of infected blood products; and vertical transmission are also recognized [3, 4, 5]. Sporadic cases reported from the developed countries are often locally contracted through food and animal meat as ''autochthonous'' or locally acquired infection [5, 6]. The incubation period ranges from 3 to 8 weeks, with a mean of 40 days. The virus is detectable in stool, bile, and liver. Stool excretion during the late incubation period lends infectivity.

Pathology

Both IgM anti-HEV during early acute infection and IgG anti-HEV predominating after the first 3 months can be detected. Antigen detection is limited to specialized laboratories through nucleic acid amplification. The typical morphologic lesions of all types of viral hepatitis are similar and consist of pan- lobular infiltration with mononuclear cells, hepatocyte necrosis, Kupffer cell hyperplasia, and variable degrees of cholestasis. In hepatitis E, a common histological feature is marked cholestasis [3, 4, 10, 11].

Clinical Complications

Most HEV infections are either asymptomatic or present as acute self limited viral hepatitis. They can be complicated by fulminant hepatitis in 1–2% of all cases and in 20% of pregnant women. Alcoholics are more prone. Patients usually present with encephalopathy, coagulopathy, ascites and edema. Cerebral edema with brain stem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in patients with deep coma). But, those who survive may have a complete recovery. Liver transplantation may be life- saving [4, 5, 11-13].

Rare complications of HEV infection reported include- pancreatitis, myocarditis, atypical pneumonia, aplastic anemia, immune thrombocytopenia, membranoproliferative glomerulonephritis, transverse myelitis, and peripheral neuropathy. There are reports of encephalopathy with CSF abnormalities too [4,5,11,12,15-17]. Lymphadenopathy is unusual and may be due to reactivation of latent EBV infection [18]. HEV co-infection with EBV, HBV, HIV, leptospirosis and salmonellosis result in a more severe clinical course [4, 5, 11, 18, 19]. These are the days of immunosuppressive therapy. Increasingly older patients are immunosuppressed from disease or treatment of rheumatologic disorders, organ transplantation and malignancies. When infected they may either have severe HEV disease or may progress to chronicity. Often, the hepatitis is initially suspected to be drug induced or auto-immune. Genotype 3 and 4 are implicated in sporadic cases [5, 6, 10, 12, 13, 18].

RBC enzyme defects like G6PD deficiency are common in certain parts of India and Africa. Such patients with HEV disease have a complicated course with hemolysis and renal failure. Tests for G6PD deficiency may be negative during the acute episode and treatment with vitamin K may worsen the hemolysis [20].

Chronicity

Progression to chronic hepatitis is suggested by (1) incomplete resolution of symptoms and persistent hepatomegaly (2) biopsy evidence of bridging or multilobular necrosis during protracted hepatitis (3) failure of liver function tests to normalize in 6–12 months; and (4) persistent antigenemia for 3 to 6 months. Chronic hepatitis E is reported not only in immunocompromised patients (organ-transplant recipients, those on cytotoxic chemotherapy and HEV- HIV co-infection); but also in immunocompetent individuals [4-6, 10-12, 21]. Genotype C is implicated in these cases. Eventually they progress to cirrhosis liver with all its related complications. One group reported a high seroprevalence of HEV in samples from cirrhotic patients where no other etiological agents were present, suggesting the potential role of HEV in chronic liver illness [10].

Vertical and transfusion related transmission

HEV-infected mothers can transmit the infection to fetus, leading to premature birth and, increased fetal loss from hypoglycemia, hypothermia, and acute hepatitis in the newborns [3, 22]. HEV and Blood Transfusion Safety is another issue that is gathering attention. As per the WHO Global Alert and Response in 2001, screening of donors showed prevalence of anti HEV antibodies of 1.4 - 2.5% in Europe, USA and South Africa; 2.8% in Thailand, 9.5% in Saudi Arabia, and 24.0% in Egypt. This did not imply infectivity. In 2014, with transfusion safety in mind, a seroprevalence survey was completed in Australia. Of 3,237 samples tested 194 (5.99%) were positive for HEV IgG, which was

comparable to Scotland (4.7%) and New Zealand (4.2%), but lower than the United States (18.8%) and southwestern France (52.5%). Detection of HEV IgM in 4 (2.06%) of the 194 samples from IgG-positive donors indicated recent infection [23]. A meta-analysis was completed in 2013 on HEV and transfusion safety. In conclusion the authors recommended a need for an agreed policy to implement HEV donor screening by blood banks so as to lower overall health care costs [24].

Treatment

Ribavirin is a nucleoside analogue effective against several DNA and RNA viruses. Hemolytic anemia is the primary adverse reaction and it falls in category X for use in pregnancy. Due to devastating consequence of end-stage liver cirrhosis in HEV infected patients, many transplant programs are instituting ribavirin therapy for persistent HEV infection. Different dosing schedules are under evaluation. In immunosuppressed patients, withdrawal or reduction of immunosuppressive drugs; administration of ribavirin; interferon; or a combination of these measures, are all under trial. A combination of ribavirin and mycophenolic acid inhibits HEV replication far more than either of the two alone [25-27].

Vaccine

Out of 11 experimental HEV vaccines evaluated in primates only 2 progressed to human clinical trials. After phase III trials, one has been developed and manufactured in China. Licensed in December 2011 for use above 16 years, it is recommended for animal husbandry workers, food handlers, students, armed forces personnel, women of childbearing age, and travellers to endemic areas. Immunization schedule is 3 doses administered at 0, 1 and 6 months [28-30]. To date it has not been licensed in other countries.

CONCLUSION

The world is moving towards becoming a global village. Given the volume of population migration, reduced travel time, increasing longevity and rising number of immunosuppressed individuals due to therapeutic interventions; the clinical importance of HEV will continue to rise. Vertical transmission, transfusion transmitted infection, zoonotic and ''autochthonous'' or locally acquired infections may eventually become as important as feco- orally transmitted ones. Rightly, it is now included amongst re-emerging infections.

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