Viral Hepatitis A & E: Introduction

Viral hepatitis,“ refers to infections that affect the liver and are caused by viruses. It is a major public health issue in the United States and worldwide. Not only does viral hepatitis carry a high morbidity, but it also stresses medical resources and can have severe economic consequences. The majority of all viral hepatitis cases are preventable.

Viral hepatitis includes five distinct disease entities, which are caused by at least five different viruses. Hepatitis A and hepatitis B (infectious and serum hepatitis, respectively) are considered separate diseases and both can be diagnosed by a specific serologic test. Hepatitis C and E comprise a third category, each a distinct type, with Hepatitis C parenterally transmitted, and hepatitis E enterically transmitted. Hepatitis D, or delta hepatitis, is another distinct virus that is dependent upon hepatitis B infection. This form of hepatitis may occur as a super-infection in a hepatitis B carrier or as a co-infection in an individual with acute hepatitis B. Hepatitis viruses most often found in the United States include A, B, C, and D.

Because fatality from hepatitis is relatively low, mortality figures are a poor indicator of the actual incidence of these diseases. The Centers for Disease Control and Prevention estimated that approximately 400,000–600,000 people were infected with viral hepatitis during the decade of the 1990s.

Hepatitis plagued mankind as early as the fifth century BC. It was referenced in early biblical literature and described as occurring in outbreaks, especially during times of war. Toward the end of the nineteenth century, hepatitis was thought to occur as a result of infection of the hepatic parenchyma. The infectious nature of hepatitis was established after World War II. In the mid-1960s, Blumberg and colleagues discovered the surface antigen and antibody of hepatitis B. This Nobel Prize-winning research opened the door to our appreciation of the morphological and immunochemical features of other forms of viral hepatitis.

What is Hepatitis A?
Hepatitis A accounts for 20–25% of the cases of clinical hepatitis in developed countries. This infection is caused by a 27 nm ribonucleic acid (RNA), cubically symmetrical picornavirus (Figure 2).

The viral antigen (HAAG) may be found in serum, stool, and the liver during the acute phase of an infection. Initially, the IgM antibody appears, but within a few weeks this antibody disappears. It is replaced by the development of IgG, which persists probably throughout life (anti-HAV). The IgM antibody is the marker for acute hepatitis A infection. IgG anti-HAV is indicative of previous exposure to the hepatitis A virus and immunity to recurrent infection. This form of hepatitis does not have a carrier state, nor does it play a role in the development of cirrhosis or chronic active hepatitis. It is an acute, self-limiting disease.

Hepatitis A is transmitted primarily through the fecal-oral route, and possibly through blood and bodily secretions. Developing countries commonly experience water- and food-borne epidemics of hepatitis A. Consumption of contaminated shellfish (raw) may also provide a route of transmission. The incidence of hepatitis A varies widely with age, socioeconomic class, geography, and other factors. The disease may occur sporadically in epidemic form.

The prognosis for patients with hepatitis A is excellent and recovery is complete. Mortality rates for large epidemics are less than 1 per 1000 population. There is no progression to a chronic disease state and there are no long-term sequelae.

What is Hepatitis E?
Hepatitis E, or enteric hepatitis, resembles hepatitis A. It is a non-A, non-B RNA virus that is enterically transmitted (fecal-oral route). This virus is endemic in India, Pakistan, China, Mongolia, Hong Kong, North Africa, and the southeast Pacific region. In the rural areas of central Mexico and Central American countries it can reach epidemic proportions. Hepatitis E affects young adults, similar to hepatitis A, and has a self-limiting course. Mortality rates in the general endemic population range between 0.5–4%, and are much higher in women during pregnancy (15–20%). Hepatitis E can also cause fetal complications, especially in the third trimester. Patients with nonfatal cases of hepatitis E have a complete recovery without chronic sequelae.

Non-A, non-B hepatitis accounts for 20–30% of the cases of clinical hepatitis in the Western world. Hepatitis E is thought to be caused by a 32 nm icosahedral non-enveloped virus in the Calicivirus family. The viral particles may be found in the stool of infected humans aggregated by antibodies during the acute and convalescent phase of infection. This form of hepatitis does not have a carrier state (Figure 3).

Symptoms
Hepatitis A and hepatitis E present with similar symptoms. Both forms of viral hepatitis may develop without clinical signs or symptoms, or nonspecific symptoms may
appear for a short time with or without jaundice. These symptoms may vary from nonspecific, flu-like symptoms to fatal liver failure. Diagnosis often depends on an accumulation of findings considered together.

Early in the disease process, the prodromal phase, some patients experience a serum-type sickness that may include fever, arthralgia, arthritis, rash, and angioneurotic edema. These symptoms usually occur 2-3 weeks before jaundice and generally subside before jaundice develops, although they may be concomitant with its appearance.

In the preicteric phase, patients may experience respiratory and gastrointestinal tract symptoms, which may include malaise, fatigue, myalgia, anorexia, nausea, and/or vomiting. They may also experience moderate weight loss, headache, coryza, fever, or pharyngitis and cough. Many patients complain of midepigastric pain, right upper quadrant discomfort, or diarrhea. Also characteristic of this phase of the disease is the development of dark urine and the lightening of stool color. The duration of this phase of the disease may range from 2–3 days to 2–3 weeks.

The icteric phase is signaled by the development of jaundice. General constitutional symptoms may subside. There may be worsening of anorexia, nausea, and vomiting along with scratching and irritated skin lesions related to pruritus.
Viral Hepatitis A & E: Anatomy

The liver is located in the right upper quadrant, from the fifth intercostal space in the midclavicular line down to the right costal margin. The liver weighs approximately 1800 g in men and 1400 g in women. The surfaces of the liver are smooth and convex in the superior, anterior, and right lateral regions. Indentations from the colon, right kidney, duodenum, and stomach are apparent on the posterior surface.

The line between the vena cava and gallbladder divides the liver into right and left lobes. Each lobe has an independent vascular and duct supply. The liver is further divided into eight segments, each containing a pedicle of portal vessels, ducts, and hepatic veins (Figure 4. A and B).

Figure 4. A, Normal gross anatomy of the liver; B, histological view.
Overview

The transmission of hepatitis A and E is primarily through person-to-person contact by fecal contamination and oral ingestion. Poor personal hygiene, poor sanitation, and intimate and/or sexual contact can facilitate the transmission. Intravenous drug use also is a risk factor in both hepatitis A and E transmission. Contaminated food and water are also sources of the virus.
Viral Hepatitis A & E: Diagnosis

History and Physical Examination
The diagnosis of hepatitis A and hepatitis E is largely dependent upon a comprehensive clinical history with particular attention given to risk factors and the physical exam. The history should focus on recent travel, exposure to water or shellfish that may have been contaminated by sewage, sexual promiscuity or homosexual activity, intravenous drug use, or other parenteral risk factors. Attention should also be given to the use of medications to ascertain if hepatotoxic drugs have been used.

Hepatitis A
The diagnosis of hepatitis A is made using serological tests that detect circulating antibodies. Anti-HAV IgM suggests recent infection, with peak levels occurring early in the infection and persisting for about 4–6 months. Anti-HAV IgG also appears early but peaks during the convalescent phase. It may be detected life-long and is responsible for protection against future infection from hepatitis A.

Hepatitis E
Hepatitis E viral particles may be detected in the stool using immune electron microscopy and by polymerase chain reaction (PCR). The serological diagnosis is made by detection of IgM, IgG, and IgA antibodies to recombinant hepatitis E viral antigens using enzyme immunoassay (EIA).

Serum Enzymes
Ornithine, carbamyltransferase, sorbitol dehydrogenase, glutamate dehydrogenase, isocitrate dehydrogenase, malate dehydrogenase, and guanase levels are all helpful in the diagnosis of viral hepatitis. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) remain the most sensitive for establishing a diagnosis of acute viral hepatitis. ALT and AST are the first enzymes to reveal abnormalities during the disease process and the last to normalize. They may reach levels 100 times the upper limits of normal, and ALT is usually more abnormal than AST in the early and late stages of the disease.

Serum Bilirubin
Bilirubin values of 2.5–3.0 mg/dl or greater establish the presence of the icteric phase of hepatitis. Bilirubin levels in excess of 30 mg/dl suggest hemolysis (over production of bilirubin) or renal failure (failure of excretion). Serum bilirubin levels are not always of clinical value.

Hematological Changes
Leukopenia is commonly observed in the presence of viral hepatitis. Anemia and thrombocytopenia are less frequently observed.
Viral Hepatitis A & E: Therapy

Overview

Hepatitis A and E usually spontaneously resolve after a period of 4–8 weeks of illness. Hepatitis A and E viruses rarely progress to chronic hepatitis. In most cases, no special treatment is necessary. Patients do not need to be confined to bed or restricted in diet or activity. Most patients may safely return to work after the resolution of jaundice (Figure 5).

Prevention

Immune globulin (IG) is an available preventive therapy for hepatitis A, and is primarily used to prevent disease after exposure. It is also used to protect travelers to areas that have a high incidence of hepatitis A. The prophylactic value of IG is greatest when given early in the incubation period. Vaccination against hepatitis A has been shown to be highly effective in preventing infection in those who have been pre-exposed to the virus.

Eradication of hepatitis E is dependent upon the provision of a clean water supply and improved hygiene and sanitation practices in developing countries. Prophylactic immunization may be possible using immunoglobulin from donors in countries with high disease prevalence. Since hepatitis E is not endemic to the United States, immunoglobulin prepared from U.S. sources is likely not to be protective. Travelers to countries where hepatitis E is endemic should be advised to avoid contaminated food and water and should not assume protection against this virus even if they have received immune serum globulin (ISG) for hepatitis A. A vaccine for hepatitis E has been developed, but has not yet been widely tested in humans.

Fulminant Hepatitis

Fulminant hepatitis is a rare syndrome usually associated with hepatitis B and is even rarer in hepatitis A or hepatitis E. It is characterized by rapid clinical deterioration and the onset of hepatic encephalopathy. Coma may develop within hours in some cases. The parenchyma of the liver suffers massive necrosis and there is marked decrease in the organ size. Hepatocellular failure and intravascular coagulation may result in bleeding. Functional renal failure may develop.

Viral hepatitis is the leading cause of fulminant hepatic failure throughout the world. Hepatitis A is directly hepatotoxic and, therefore, diminished host defenses and unusually large inoculum may contribute to fulminant hepatic failure. Other factors increasing the likelihood of development of fulminant hepatic failure include hepatitis A viral infection in individuals over 40 years of age, hepatitis A superimposed on pre-existing liver disease, and travel to areas with high endemicity. Hepatitis E is not considered a major cause of fulminant hepatic failure in western countries but should be considered in patients who have returned from endemic regions.

Careful management and painstaking nursing care of specific complications provides the best hope for recovery. Infection control and, in some instances, reverse isolation should be included in the general management of patients with fulminant hepatic failure.

Regular monitoring of blood glucose levels with constant glucose infusion is essential in these patients since hypoglycemia is a constant threat. Monitoring of weight and serum electrolytes is crucial because of the reduction in sodium and free water clearance. Early in the course of fulminant hepatic failure, potassium supplementation is usually required. Hemoperfusion or hemodiafiltration is required when there is significant renal dysfunction.

The degree of hepatic encephalopathy (grade) is a reasonable indicator of prognosis. However, encephalopathy alone is not a threat to the patient. Administration of lactulose may be useful in improving hepatic encephalopathy, but should be administered with care since it may cause electrolyte abnormalities.

Intracranial pressure (ICP) monitoring is essential in fulminant hepatic failure. As the grade of encephalopathy increases (Grade III–IV), intracranial hypertension becomes a serious problem. The risk of brain damage begins when ICP reaches 25 mm Hg. In addition, cerebral perfusion pressure should be maintained above 50 mm Hg to assure adequate perfusion to the brain. Recent studies have shown that monitoring of intracranial pressure has resulted in interventions to lower ICP. These interventions resulted in longer survival and also allowed additional time for spontaneous recovery in a small group of patients. In many cases this improved survival proved essential in the context of liver transplantation.

Intracranial hypertension management should also include head elevation, hyperventilation, diuresis, and drug-induced coma. Head elevation above 20 degrees is not recommended as it has been demonstrated to cause a fall in cerebral perfusion pressure and a rise in ICP. Hyperventilation is a common therapy and may be useful in short-term treatment. Maintenance of the pCO2 above 24 mm Hg is recommended, as cerebral vasoconstriction is associated with lower levels. Loop diuretics and osmotic agents (such as furosemide and mannitol) are used to treat elevated intracranial pressures or the clinical signs of cerebral edema. Mannitol is the preferred drug and should be administered in a dose of 0.5–1 g/kg over 5 minutes. Thiopental or pentobarbital may be used to treat unresponsive intracranial hypertension. These agents are initially administered as a bolus and followed by continuous infusion.

Hypotension is a frequent problem in the management of patients with fulminant hepatic failure. Hemodynamic monitoring is essential to maintain cerebral perfusion pressure above 50 mm Hg and optimize cardiovascular function (including cardiac index > 4.5 L/min/m2, oxygen delivery > 800 L/min/m2, and oxygen consumption > 150 L/min/m2). Epinephrine and norepinephrine are the vasoressors of choice, as they increase both systemic vascular resistance and cardiac output. However, these agents may worsen tissue hypoxia. N-acetylcysteine and/or prostacyclin provide blood pressure support (although they are not currently available in the United States). In the absence of these agents, blood pressure support must take precedence in the hierarchy of management of patients with fulminant hepatic failure.

Cardiovascular management includes maintenance of renal perfusion, which may be achieved with low-dose dopamine (2–4 μg/kg/h), though dopamine will not prevent a renal shutdown. Renal support should be introduced if volume or electrolyte management dictates. Continuous arteriovenous hemoperfusion or veno-venous hemoperfusion and hemodialfiltration are preferred methods of providing renal support. Anticoagulation of the patient with heparin (to assure an activated clotting time of 200–250 sec) is recommended.

Liver transplantation has become the standard of care in many institutions. Given the reliability of prognostic indicators, and the high morbidity in patients with fulminant hepatic failure, orthotopic liver transplantation offers a survival rate of close to 90% with stringent selection criteria.

For more information: Johns Hopkins Liver Transplantation Website