Viral hepatitis A, E

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VIROLOGY AND ETIOLOGY

- **Hepatitis A.** Hepatitis A virus is a nonenveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the hepatovirus genus of the picornavirus family. Its virion contains four capsid polypeptides, designated VP1 to VP4, which are cleaved posttranslationally from the polyprotein product of a 7500-nucleotide genome. Inactivation of viral activity can be achieved by boiling for 1 min, by contact with formaldehyde and chlorine, or by ultraviolet irradiation. Despite nucleotide sequence variation of up to 20% among isolates of HAV, all strains of this virus are immunologically indistinguishable and belong to one serotype.

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- Hepatitis A has an incubation period of approximately 4 weeks. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent. HAV can be cultivated reproducibly in vitro. Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAVshedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several months, rarely for 6 to 12 months.

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- During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody. Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class. After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection.

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Hepatitis E. Previously labeled *epidemic* or *enterically transmitted non-A, non-B hepatitis*, HEV is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America. This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, nonenveloped, HAV-like virus with a 7600-nucleotide, single-stranded, positive-sense RNA genome. HEV has three open reading frames (genes), the largest of which encodes nonstructural proteins involved in virus replication. A middle-sized gene encodes the nucleocapsid protein, and the smallest, whose function is not known, encodes protein specificities to which antibodies appear in human serum.

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- All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25%. There is no genomic or antigenic homology, however, between HEV and HAV or other picornaviruses; and HEV, although resembling calciviruses, appears to be sufficiently distinct from any known agent to merit a new classification of its own within the alphavirus group. The virus has been detected in stool, bile, and liver and is excreted in the stool during the late incubation period; immune responses to viral antigens occur very early during the course of acute infection. Both IgM anti-HEV and IgG anti-HEV can be detected, but both fall rapidly after acute infection, reaching low levels within 9 to 12 months. Currently, serologic testing for HEV infection is not available routinely

EPIDEMIOLOGY

Hepatitis A *This agent is transmitted almost exclusively by the fecaloral route*. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding; large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, frozen raspberries and strawberries, and shellfish. Intrafamily and intrainstitutional spread are also common. Early epidemiologic observations suggested that there is a predilection for hepatitis A to occur in late fall and early winter. In temperate zones, epidemic waves have been recorded every 5 to 20 years as new segments of nonimmune population appeared; however, in developed countries, the incidence of hepatitis A has been declining, presumably as a function of improved sanitation, and these cyclic patterns are no longer being observed.

EPIDEMIOLOGY

No HAVcarrier state has been identified after acute hepatitis A; perpetuation of the virus in nature depends presumably on nonepidemic, inapparent subclinical infection.

In the general population, anti-HAV, a marker for previous HAV infection, increases in prevalence as a function of increasing age and of decreasing socioeconomic status. In the 1970s, serologic evidence of prior hepatitis A infection occurred in about 40% of urban populations in the United States, most of whose members never recalled having had a symptomatic case of hepatitis. In subsequent decades,

however, the prevalence of anti-HAV has been declining in the United States. In developing countries, exposure, infection, and subsequent immunity are almost universal in childhood.

EPIDEMIOLOGY

As the frequency of subclinical childhood infections declines in developed countries, a susceptible cohort of adults emerges. Hepatitis A tends to be more symptomatic in adults; therefore, paradoxically, as the frequency of HAV infection declines, the likelihood of clinically apparent, even severe, HAV illnesses increases in the susceptible adult population. Travel to endemic areas is a common source of infection for adults from nonendemic areas. More recently recognized epidemiologic foci of HAV infection include child-care centers, neonatal intensive care units, promiscuous homosexual men, and injection drug users. Although hepatitis A is rarely bloodborne, several outbreaks have been recognized in recipients of clotting factor concentrates.

EPIDEMIOLOGY

Hepatitis E. This type of hepatitis, identified in India, Asia, Africa, and Central America, resembles hepatitis A in its primarily enteric mode of spread. The commonly recognized cases occur after contamination of water supplies such as after monsoon flooding, but sporadic, isolated cases occur. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Infections arise in populations that are immune to HAV and favor young adults. It is not known if hepatitis E occurs outside of recognized endemic areas, for example, in the United States, but preliminary studies suggest that HEV does not account for any of the sporadic “non-A, non-B” cases in nonendemic areas. Cases imported from endemic areas have been found in the United States. Several reports suggest a zoonotic reservoir for HEV in swine.

Symptoms and Signs

Acute viral hepatitis occurs after an incubation period that varies according to the responsible agent. Generally, incubation periods for hepatitis A range from 15 to 45 days (mean 4 weeks), and for hepatitis E from 14 to 60 days (mean 5 to 6 weeks). The *prodromal symptoms* of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1 to 2 weeks. The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38 and 39 C (100 to 102 F) is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a serum sickness–like syndrome; rarely, a fever of 39.5 to 40 C (103 to 104 F) may accompany the constitutional symptoms.

Symptoms and Signs

Dark urine and clay-colored stools may be noticed by the patient from 1 to 5 days before the onset of clinical jaundice.

With the onset of *clinical jaundice*, the constitutional prodromal symptoms usually diminish, but in some patients mild weight loss (2.5 to 5 kg) is common and may continue during the entire icteric phase.

The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction.

Splenomegaly and cervical adenopathy are present in 10 to 20% of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence.

Symptoms and Signs

During the *recovery phase*, constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the posticteric phase is variable, ranging from 2 to 12 weeks. Complete clinical and biochemical recovery is to be expected 1 to 2 months after all cases of hepatitis A and E and 3 to 4 months after the onset of jaundice in three-quarters of uncomplicated cases of hepatitis B and C. In the remainder, biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric.

Laboratory Features

The serum aminotransferases aspartate aminotransferase (AST) and ALT show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. Peak levels vary from 400 to 4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis. The diagnosis of anicteric hepatitis is based on clinical features and on aminotransferase elevations.

Laboratory Features

Jaundice is usually visible in the sclera or skin when the serum bilirubin value exceeds 43 mol/L (2.5 mg/dL). When jaundice appears, the serum bilirubin typically rises to levels ranging from 85 to 340 mol/L (5 to 20 mg/dL). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. Bilirubin levels 340 mol/L (20 mg/dL) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease.

Laboratory Features

In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed hemolysis. In such patients, bilirubin levels 513 mol/L (30 mg/dL) have been observed and are not necessarily associated with a poor prognosis.

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%) are common during the acute phase. Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis.

Laboratory Features

Occasionally, a prolonged PT may occur with only mild increases in the serum bilirubin and aminotransferase levels. Prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycemia noted occasionally in patients with severe viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon in uncomplicated acute viral hepatitis. In some patients, mild and transient steatorrhea has been noted as well as slight microscopic hematuria and minimal proteinuria. Serologic tests are available with which to establish a diagnosis of hepatitis A. Tests for fecal or serum HAV are not routinely available. Therefore, a diagnosis of hepatitis A is based on detection of IgM anti-HAV during acute illness. Rheumatoid factor can give rise to false-positive results in this test.

COMPLICATIONS AND SEQUELAE

A small proportion of patients with hepatitis A experience *relapsing hepatitis* weeks to months after apparent recovery from acute hepatitis. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasionally jaundice, and fecal excretion of HAV. Another unusual variant of acute hepatitis A is *cholestatic hepatitis*, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities persist for many months, even up to a year. Even when these complications occur, hepatitis A remains self-limited and does not progress to chronic liver disease.

Treatment

- Specific therapy is unknown.
- Mild viral hepatitis in their acute phase should be treated by adequate regimen, diet, and sparing conditions for the liver. During the first 7-10 days of clinical jaundice, the patient must remain in bed but later he can occasionally leave his bed. The diet should be sparing but adequate. The daily ration must include at least 100 g protein, to 30-40 g of butter, and carbohydrates. Fried, smoked or pickled food, and also alcohol should be excluded. Food must be rich in vitamins. Taking much liquid (2-3 litres a day) as stewed fruits, tea with lemon, fruit juices, and the like, is recommended. Daily evacuation of the bowels is necessary.
- Patients with moderate disease attended with signs of toxaemia, who are unable to drink great quantity of liquid because of nausea, should be given detoxicating therapy. A 5-10 per cent glucose solution, Ringer-Locke solution (250-500 ml each) with an addition of 10 ml of a 5 per cent ascorbic acid solution should be given by drip infusion. Nicotinic acid (60 mg), thiamine (6 mg), riboflavin and pyridoxine should also be given. If necessary, neohaemodez or rheopolyglucin (200-400 ml), plasma (100-150 ml) or the like should be administered.

Treatment

- Patients with severe forms of the disease should be moved to an intensive therapy unit or other ward where they can be properly observed by a neurologist (twice a day). Their acid-base and water-salt equilibria should be controlled; coagulograms should be taken, and daily diuresis measured. Detoxicating preparations should be given. Oliguria should be treated with furosemide (0.02- 0.04 g) in combination with verospiron (0.025 g 3-4 times a day). In order to eliminate hypokalaemia, panangin (10-20 ml) should be administered. Vikasol (1 per cent solution, 2-5 ml) should be given intramuscularly for haemorrhage. Prednisolone is indicated of encephalopathy. Patients with acute hepatic ncephalopathy should be restricted in protein; they should be given cleansing enema with subsequent intestinal lavage with a 4 per cent sodium bicarbonate solution. Complications are prevented by antibiotics. If signs of brain oedema develop, dehydration therapy is indicated in addition to detoxicating treatment. Inhibitors of proteolytic enzymes (gordox, trasylol) in mean therapeutic doses (10000-30000 U) give a positive effect.

PROPHYLAXIS

Hepatitis A Both passive immunization with IG and active immunization with killed vaccines are available. All preparations of IG contain anti-HAV concentrations sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent hepatitis A. For postexposure prophylaxis of intimate contacts (household, sexual, institutional) of persons with hepatitis A, the administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure. Prophylaxis is not necessary for casual contacts (office, factory, school, or hospital), for most elderly persons, who are very likely to be immune, or for those known to have anti-HAV in their serum. In day-care centers, recognition of hepatitis A in children or staff should provide a stimulus for immunoprophylaxis in the center and in the children's family members.

PROPHYLAXIS

By the time most common-source outbreaks of hepatitis A are recognized, it is usually too late in the incubation period for IG to be effective; however, prophylaxis may limit the frequency of secondary cases. For travelers to tropical countries, developing countries, and other areas outside standard tourist routes, IG prophylaxis had been recommended, before a vaccine became available. When such travel lasted less than 3 months, 0.02 mL/kg was given; for longer travel or residence in these areas, a dose of 0.06 mL/kg every 4 to 6 months was recommended.

Hepatitis A vaccine has been reported to be effective in preventing secondary household cases of acute hepatitis A, but its role in other instances of postexposure prophylaxis remains to be demonstrated.

PROPHYLAXIS

Hepatitis E. A recombinant vaccine has been developed and is undergoing clinical testing.