BRIEF REVIEW

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Hepatitis A Virus: a Major Global Public Health Problem, Especially in Developing Countries

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Introduction

Hepatitis A is the most common cause of acute viral hepatitis worldwide[1]. The Recent development of two highly effective vaccines offers an opportunity for the prevention of symptomatic hepatitis A virus (HAV) infection although cost is a significant issue for mass immunization worldwide.

Epidemiology

The incidence and prevalence of HAV varies by ethnicity and age worldwide. South America, Africa, India, the Middle East and Asia have high seroprevalence rates, and the United States and Japan have relatively low rates. Persons aged 5 to 14 years are more likely to have acute HAV. During community-wide outbreaks; however, HAV is not limited to specific age groups, and sustained nationwide reductions in incidence are likely to require routine childhood immunization rather than focused high-risk group vaccination[2].

The following features of HAV infection favor rapid spread and large outbreaks:

1) Very young children are often asymptomatic thus creating a natural reservoir for HAV.
2) HAV-infected adults are symptom free during the incubation period, when HAV shedding levels are the highest.

Large epidemics of hepatitis A occurs every 10 years in the United States and has a stable lower level of prevalence between epidemics.

The most frequently reported sources of hepatitis A infection are household or sexual contact (22-26%), day care attendees or employees (14-16%), contacts during international travel (5%), contaminated food and water (5%), and in approximately 50% of cases no identifiable source is found[3].

The overall case fatality rate is approximately 0.3%. HAV infection results in substantial morbidity with associated costs of medical coverage and loss; in 1989, the last epidemic of the USA, estimated annual cost was over $200 million .

Virology

HAV is a 27-mm non-enveloped RNA virus of hepatitis genus in picornavirus family. HAV is thermostable, acid resistant, and most importantly, resistant to bile lysis because the virus has no lipid envelope. This latter capacity allows efficient fecal-oral transmission. There are four genotypes but only one serotype.

Pathogenesis

The major mechanism of HAV infection is oral inoculation of fecally excreted virus, making this disease in principle preventable through public health measures. After oral inoculation of HAV, it is transported across the intestinal epithelium by means of a poorly understood transport system and travels in the mesenteric veins to the liver where it is taken up by hepatocytes. In hepatocytes, HAV replication occurs by a mechanism involving an RNA-dependent polymerase. HAV is shed from

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hepatocyte to sinusoids and bile, then into the intestine through bile, where it is excreted in feces. Alternatively, HAV can be transmitted through blood (intravenous drug use and blood transfusions in humans and experimentally in primates) with an unknown efficiency.

The mechanism of hepatocyte injury in HAV is not proven, but direct and indirect evidence suggests a cell-mediated immune mechanism CD8+ (MHC-class I), cytotoxic T cell (CTL), which are found in liver at the site of injury and in the peripheral blood of infected patients [4, 5]. They are capable of killing infected antilogous cells specifically .

Secreted cytokines (especially IFN-α) may aid in recruiting other inflammatory cells to the sites of infection, and indirectly increase hepatocyte injury[6]. The process of eliminating HAV, probably involves a combinations of antibody-mediated clearance, interferon-mediated inhibitions of replication, and CTL-induced apoptosis. Both IgM and IgG antibodies have virus-neutralizing activities and anamnestic IgG responses have been documented with re-infection [7].

Clinical features

HAV is generally an acute disease, with rare but documented relapsing cases. As compared with HBV and HCV, uncommon extrahepatic manifestations occur (e.g. vasculitis). No chronic sequelae occur from HAV once it is resolved, with the exception of an extremely rare HAV-related nephritic syndrome and consequent chronic renal insufficiency. Furthermore, in contrast to hepatitis B, a chronic carrier state does not exist for HAV. A helpful fact in diagnosis of HAV is its incubation period of 28 days (ranging 15-45 days)

The most important determinant that affects the severity of illness is age. For example, about 70% of adults are symptomatic compared to 30% of children and adolescents.

Symptomatic patients have four main clinical presentations:

1) The onset of classic-HAV is typically abrupt with a mild prodromal illness of fever, headache, malaise, fatigue and nonspecific gastrointestinal symptoms. Nausea, vomiting and diarrhea occur about 1 week before the onset of dark urine, which is the most specific sign that causes most patients to seek medical attention. This is usually followed within a few days by pale or clay-colored stool and jaundice.
   Physical examination reveals tender hepatomegaly, splenomegaly, and post cervical lymphadenopathy, which heralds the resolution of the prodromal symptoms (i.e. the convalescent phase).
   This classical presentation, which occurs in 80% of symptomatic patients, is self -limited and lasts less than 8 weeks. A small subset of patients present with extrahepatic manifestations such as vasculitis, arthritis, cryoglobulinemia, mononeuritis multiplex, hemolytic anemia, or acalculus cholecystitis[8].
2) Relapsing hepatitis A accounts for about 4-20% of symptomatic patients. Clinically, these patients are recognized by two or more bouts of acute HAV over a 6- to 10-week period, with symptom free intervals.
3) Cholestatic hepatitis A occurs in 10% of patients with symptomatic disease[9]. It is characterized by a prolonged course (several months) with fever, marked pruritus, and jaundice, during which the aminotransferase and alkaline phosphatase levels gradually fall to normal , but serum bilirubin remains elevated.
4) Fulminant hepatitis A is the most severe form of symptomatic HAV and can lead to emergent need for liver transplantation [10] although it accounts for only 0.35% of cases. Clinically, this syndrome is characterized by worsening jaundice, encephalopathy and prolongation of prothrombin time, usually in the first week (55% of cases) and almost always in the first month (90% of cases) following the onset of the disease[11]. Elderly patients and patients with chronic liver disease 12, 13 are at a higher risk of fulminant hepatic failure from acute HAV. The case fatality rate in adults over the age of 50 years is 70%, which is much higher than the rate of 0.3% for all ages. Mortality rates in patients with chronic liver disease were as high as 60 times those of patients without previous liver disease [1]. These data suggest an important role for HAV vaccination in those with chronic hepatitis B and C. Unlike hepatitis E, acute HAV has shown no evidence yet of an increased case fatality rate in pregnancy.

Diagnosis

The diagnosis of acute hepatitis A infection is made by detection of IgM anti HAV in an appropriate context. HAV-RNA can be detected in body fluids and serum using PCR amplification, but this test is expensive and used primarily for research purpose. IgM anti-HAV is detected 1 to 2 weeks after exposure to HAV and persists for 3-6 months. HAV IgG is detectable 5 to 6 weeks after exposure (i.e. during the convalescent phase of acute hepatitis

A infection). It persists for decades after acute infection, and confers lifelong protection against HAV.

The total anti-HAV measures both IgM and IgG. A positive total anti-HAV with a negative IgM anti-HAV indicates immunity consistent with either past infection or vaccination. Serum aminotransferases (especially ALT) may reach levels as high as 5000 IU/L, but elevation does not correlate with disease severity or prognosis. Alkaline phosphatase usually is only minimally elevated and the total bilirubin level is rarely higher than 10mg/dl except in the cholestatic form of acute hepatitis A and in those with fulminant hepatitis A. A prolonged prothrombin time reflects extensive hepatocellular necrosis and can predict higher mortality. Liver biopsy is not required to establish the diagnosis of acute hepatitis A.

Treatment

Virus specific therapy is not available for HAV but acute infection can be prevented with immunoglobulin treatment within 2 weeks of exposure, or use of an FDA-approved HAV vaccine within 3 to 4 weeks of travel. Once acute disease occurs, management is usually on an outpatient basis. Indications for hospitalization are as follows: dehydration, severe prostration, coagulopathy, encephalopathy, or other evidence of hepatic decompensation[2]. Patients at increased risk for severe outcomes include the elderly (with or without comorbid disease) and patients with chronic liver disease, especially hepatitis C-related liver disease.

Most patients experience complete clinical and biochemical recovery within 3 to 6 months from the onset of disease. Treatment is largely supportive. Bed rest and balanced nutrition are recommended, but patients can resume their activity as soon as they perceive improved energy levels without obvious risk for decompensation on prolongation of disease. Generally, patients should avoid alcohol and other hepatotoxins (e.g. more than 2g/d of acetaminophen). Patients with cholestatic hepatitis A have been treated with short courses of corticosteroids, but no objective evidence exists that this improves the outcome. Clinical parameters predicting a less favorable outcome include marked prolongation of the prothrombin time (PT>35 seconds) or at least three of following: age less than 10 years or greater than 40 years, PT greater than 25 seconds, bilirubin greater than 17mg/dl or a period from jaundice to encephalopathy longer than 7 days (modified from King's College criteria) [14, 15].

Patients with fulminant hepatic failure should be followed more carefully by being monitored in an intensive care unit (ICU) and emergent evaluation for potential liver transplantation.

Prophylaxis

Because no specific treatment is available for acute hepatitis A, prevention by immunization is emphasized, especially for children in high prevalence areas and adults at risk for more severe HAV -those over the age of 49 years and those with chronic liver disease. Considering the costly alternative of liver transplantation, prevention of acute HAV in these groups strongly seems likely to be cost-effective.

Two forms of immunization are available: passive immunization with immune globulin (IG) and active immunization with inactivated vaccines (Havrix and Vaqta). Passive immunization using IG is recommended in the following [16]:

1) All household and sexual contacts of persons with serologically confirmed hepatitis A.
2) All staff and attendees of day care centers or homes if one or more cases of hepatitis A are recognized in children or employees or cases are recognized in two or more households of center attendees.
3) If a food handler is diagnosed with hepatitis A, IG should be administered to other food handlers and to patrons only if the food handler directly handled uncooked or cooked foods when the handler was likely to be infected (and had diarrhea or poor hygienic practices). Patrons can be identified and treated within 2 weeks of exposure.
4) Persons who travel to countries that have high or intermediate rates of endemic infection and those whose travel is within 4 weeks. IG is also recommended for travelers under 2 years of age because the inactivated vaccine currently is not licensed for use in this age group.

Routine passive immunization is not indicated in hospital personnel, persons with causal contact with a person with hepatitis A, or when a single case occurs in an elementary or secondary school, office, or other work settings.

When administrated for pre-exposure prophylaxis, a dose of 0.02 cc/kg confers protection for up to 3 months, and a dose of 0.06 cc/kg for up to 5 months. After exposure, the dose is 0.02cc/kg, and should be administered within 2 weeks of exposure, when its efficacy is greater than 85%.

IG is administered intramuscularly, and should not be administered within 2 weeks of administration of live, attenuated vaccines (e.g.

measles, mumps, rubella, varicella) because IG decreases the immunogenecity of these vaccines. The immunogenecity of the inactivated HAV vaccines is not affected by concurrent IG administration.

The two HAV vaccines licensed in the United States are Havrix and Vaqta. Both vaccines are derived from formalin inactivation of cell culture-propagated HAV. Havrix contains a preservative (2-phenoxyethanol) whereas Vaqta does not. Both are administered intramuscularly as two injections given 6 months apart. They are not yet approved for children under 2 years of age. Furthermore, the degree of maternal transfer of protective antibody is not known in this age group. Efficacy and immunogenecity are similar for both products although the geometric mean titers of anti-HAV antibody tend to by higher with Vaqta. In most clinical studies levels greater than 20 mIU/L with Havrix and 10mIU/L with Vaqta are defined as protective antibody response.

Protective antibody levels are achieved in 88% and 99% of adults given Havrix and 95% and 100% of adults given Vaqta at 1 month and 7 months, respectively. These levels of antibody titers are estimated to confer protection for at least 5 to 10 years and perhaps longer. No clinical case of HAV has been documented as long as 6 years after immunization with Vaqta despite a documented high rate of community exposure in the studied population[17]. Both vaccines are generally well tolerated. All vaccines should be observed for anaphylaxis because although rare, it has been reported after initial and subsequent doses of HAV vaccine.

As with hepatitis B vaccines, possible associations with demylinating syndromes have been noted in post-licensure reports (e.g. Guillain-Barre syndrome, transverse myelitis, and multiple sclerosis)

The frequency of Guillain-Barre syndrome is not different in those vaccinated versus the rate expected in an unvaccinated population (CDC1 unpublished data) and the long-term relevance of the associations is not clear at this time [3].

Active immunization using the available HAV vaccine is recommended in the following:

1) Persons traveling to or working in countries or communities with high or intermediate rates of infection, including during outbreaks in such areas.
2) Children over the age of 2 years in communities that have high rates of hepatitis A and periodic hepatitis A outbreaks.
3) Men who have sex with men.
4) Injection and non-injection uses of illicit drugs if local epidemiologic and surveillance data indicate current or past outbreaks among these groups. Because a high proportion of injection drug users have hepatitis C, HAV vaccination is justified for this group.
5) Persons who work with HAV-infected primates or with HAV itself in a research laboratory (occupational risk)
6) Persons with chronic liver disease and for patients before and after liver transplantation[18]. Although not at increased risk for HAV infection, these patients are at increased risk of fulminant hepatitis A, with an estimated case fatality rate of 4.6. [11, 8]
7) Several outbreaks of hepatitis A have been reported among persons with clotting factor disorders who had been given solvent detergent-treated factor VIII and concentrates.
8) HAV vaccination was shown to be effective in preventing secondary infection of HIV in household and personal contacts of people with sporadic HAV infections.

Combined passive and active immunization can be administered, but care should be taken to use different injection sites for each. This offers immediate protection, but lowers the post-vaccination protective antibody levels. Because HAV infection leads to lifelong immunity, and 33% of people in the United States are anti-HAV positive, it would be cost effective to check serology before vaccination in the following populations [3]:

1) Adults who were born or lived for extensive period in geographical areas that have high rates of HAV.
2) Older adolescents and adults in certain population groups (e.g. American Indians , Alaskan natives , and Hispanic Americans)
3) Adults in certain groups with high prevalence of HAV infection (e.g. men who have sex with men, especially if over the age of 40 years)

Post-vaccination testing is not recommended because of the high rates of vaccination response (nearly all adults and children above 2 years of age seroconvert) and because tests that have the sensitivity to detect low anti-HAV concentrations are not approved for routine use.

An analysis of the cost-effectiveness of HAV vaccination strategies using Markov decision-modeling techniques suggests that it would not be cost-effective to vaccinate either the whole population or only individuals with negative HAV antibody unless changes occurred in HAV incidence [19].

Such conditions might exist in areas where HAV is endemic, or under mass-vaccination scenarios, or if the cost of a single dose of vaccine approaches $ 7.

Summary

Worldwide, HAV remains an important cause of community-acquired hepatitis. In recent years, improvements in personal hygiene and environmental sanitation have led to declines in overall hepatitis A infection rates in developed countries, although sporadic outbreaks still occur with similar rates of hospitalization and loss of work. Therapy remains supportive and prevention holds the key to elimination of widespread infection.

Acute infection can be prevented or attenuated with IG or with inactivated, high immunogenic vaccines. Elderly persons and those with advanced liver disease are at higher risk of the consequences of acute HAV, and they represent target populations for immediate vaccination.

Challenges for the future include strategies for broad-based population vaccination, including cost-effective approaches.

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