

Part 1

The Basics

Chapter 1: Hepatitis A - Epidemiology, transmission and natural history

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Genomic Organisation

The hepatitis A virus was identified in 1973 (Feinstone 1973). It is a 27 nm, positive-stranded RNA, non-enveloped, icosahedral virus of the heparnavirus genus of the Picornaviridae. Its viral genome contains 7474 nucleotides that are grouped into three regions: a 5' and a 3' non-coding region and a 6681 nucleotide open reading frame. The polypeptide encoded by the open reading frame is processed by a viral protease, resulting in eleven proteins of which four are structural and seven are non-structural. Four distinct HAV genotypes in humans have been identified, although significant biological differences have not been found (Lemon 1992).

Epidemiology

Hepatitis A infection occurs worldwide sporadically or in epidemic outbreaks. There is an estimated caseload of 1.4 million cases per year (Viral Hepatitis Prevention Board 1997). As it is transmitted and spread via the faecal-oral route (Hollinger 1996), it shows higher prevalence in areas with low socio-economic status where adequate sanitation or adequate hygienic practices are lacking. The incidence of 1.5 per 100,000 in industrialised countries, e.g., the United States or Germany (Wasley 2007; RKI 2006), is low compared to developing countries (parts of Africa, Asia, Central and South America) where it may reach up to 150 per 100,000 per year (WHO).

Transmission

HAV is generally acquired via the faecal-oral route either by person-to-person contact or ingestion of contaminated food or water, as well as sexually via anilingus. Hepatitis A is an enteric infection spread by contaminated excreta. High concentrations of virus are shed in the stools of patients 3 to 10 days prior to the onset of illness and until one to two weeks after the onset of jaundice. Faecal excretion of HAV persists longer in children and in immunocompromised persons (up to 4 to 5 months after infection) (Hollinger 1996).

Persons in psychiatric institutions or day-care centres, health care providers, military personnel and men who have sex with men (especially when practicing anal intercourse) are at higher risk of infection. Parenteral transmission via IV drug use or transfusion of blood products is rare because of the short period of HAV viraemia during acute infection. Mother-to-foetus transmission has not been reported.

Clinical course

Hepatitis A infection can take a wide spectrum of clinical courses ranging from asymptomatic or subclinical infection to cholestatic presentation or even to fulminant liver failure. In children most infections are asymptomatic, while in adults 70% show clinical illness. Anicteric symptomatic HAV is more frequent than icteric disease, as only 30% of patients develop jaundice.

The incubation time averages 30 days (15 to 49 days). The illness begins with the abrupt onset of unspecific prodromal symptoms including fatigue, malaise, nausea, vomiting, anorexia, fever, abdominal discomfort, and right upper quadrant pain (Lednar 1985). Within one week, patients with an icteric course note darkened urine, light-coloured acholic stool, jaundice, and often pruritus. The prodromal symptoms usually diminish when jaundice appears. The jaundice is most intense typically within the first two weeks. Decrease and subsequent normalisation of serum aminotransferases occurs rapidly and before a decrease or normalisation of serum bilirubin.

A biphasic or relapsing form of viral hepatitis A occurs in 6-10% of cases. The initial episode lasts 3-5 weeks and is followed by a period of remission characterised by normal liver chemistries lasting 4-5 weeks. Relapse may mimic the initial episode of the acute hepatitis. The full duration of the illness ranges from 16-40 weeks from the onset, and HAV-IgM antibodies persist throughout the clinical course (Schiff 1992).

A severe fulminant course of HAV with hepatic failure is found more often in patients with underlying liver disease. Patients with chronic hepatitis C have a greatly increased risk of hepatic failure, while HBV coinfection is less perilous (Vento 1989). Other risk factors are age, malnutrition and immunosuppression.

The available data on HAV in pregnant women is not conclusive. Some data show a risk of gestational complications and premature birth (Elinav 2006; Zhang 1990) while others have not observed such complications (Tong 1981).

Hepatitis A infection has been reported as a trigger for autoimmune chronic active hepatitis (CAH) in genetically susceptible individuals (Vento 1991). In 58 monitored relatives of patients with CAH, three cases of subclinical HAV occurred. Two of these developed CAH within 5 months of HAV infection. Both showed a defective T cell control of immune responses to the asialoglycoprotein receptor with ongoing T helper cell activation after the clearance of HAV.

Overall, a lethal course of HAV occurs in 0.1% of children, in 0.4% of persons aged 15-39 years, and in 1.1% in persons older than 40 years (Lemon 1985). Although a relapsing form of HAV (mentioned above) is known, the infection does not progress to a chronic state.

Clinical presentation

Jaundice and hepatomegaly are the two main findings in a physical examination. They are seen in 70 and 80% of symptomatic patients, respectively (Tong 1995). Other findings are splenomegaly, evanescent rash, cervical and other lymphadenopathies.

Extrahepatic manifestations

Although less frequent than in HBV infection, extrahepatic manifestations have been associated with acute HAV infection (Schiff 1992). Cutaneous vasculitis is typically located on the legs and buttocks. Skin biopsies reveal the presence of anti-HAV IgM and components of the complement system in the blood vessel walls. Also, arthritis appears to have a predilection for the lower extremities. Both arthritis and vasculitis have been associated with cryoglobulinaemia. Manifestations in the nervous system such as transverse myelitis, optic neuritis, and polyneuritis may also be immunocomplex-related. Haematological complications include thrombocytopenia, aplastic anaemia, and red cell aplasia. These conditions appear to be more likely in patients with prolonged symptoms.

Laboratory findings

In symptomatic patients typical laboratory findings are marked elevations of serum aminotransferases, alkaline phosphatase, and serum bilirubin (Tong 1995). Serum alanine aminotransferase (ALT) usually shows higher values than serum aspartate aminotransferase (AST) and concentrations exceeding 1000 IU/L are common.

The increase of serum aminotransferase precedes the elevation of serum bilirubin and the peak of bilirubin concentration occurs after the peak of aminotransferase concentration. Serum bilirubin often exceeds a concentration of 10 mg/dl. Other laboratory abnormalities include elevations of acute phase reactants, an elevated erythrocyte sedimentation rate, and increased immunoglobulins.

Diagnosis

The specific diagnosis of acute HAV infection is made by the detection of serum anti-HAV IgM antibodies in those with symptoms of acute hepatitis. This antibody is present in 99% of patients by the time of appearance of clinical symptoms. Therefore, it is the gold standard for detection of acute HAV. Anti-HAV IgM concentration peaks in the second month of infection and then gradually decreases until it becomes undetectable, usually after 6 to 12 months. Sometimes anti-HAV IgM persists longer and therefore, detection in asymptomatic individuals does not necessarily indicate acute infection, as it could be an effect of previous asymptomatic HAV contact (CDC 2005).

Detection of HAV in stool, body fluids, serum and liver tissue by either electron microscopy or polymerase chain reaction (PCR) is more complicated and expensive. Anti-HAV IgG antibodies are formed in the early convalescent phase, remain positive for decades, and provide long-lasting, if not lifetime immunity to re-infection.

Treatment

Because acute hepatitis A is a self-limiting disease and in most cases resolves spontaneously without residual damage or sequelae and no specific therapy is available, the treatment is based on monitoring. In 85% of cases, clinical symptoms and laboratory abnormalities resolve within 3 months. After 6 months almost all patients have complete recovery (Koff 1992). More severe courses require hospitalisation. In an outbreak in Pennsylvania, USA, 20% of patients had to be admitted to hospital (Wheeler 2005). The rare cases that progress to fulminant hepatic failure (impaired synthetic function, hepatic encephalopathy) require aggressive monitoring therapy. These patients should be transferred to a centre that is capable of performing liver transplantation.

Prevention

HAV is predominantly transmitted faecal-orally by ingestion of contaminated foods and water. Therefore proper preparation of foods especially in areas where HAV is endemic is crucial to avoid infection (“cook it, peel it, or leave it”). A second option is vaccination. There are several effective and highly immunogenic vaccines commercially available (Hammit 2008). The issue is discussed in more detail in Chapter 7, ‘Prophylaxis and vaccination of viral hepatitis’.

References

- CDC (Centers for Disease Control). Positive test results for acute hepatitis A virus infection among persons with no recent history of acute hepatitis. *MMWR* 2005; 54: 453-6.
- Elinav E, Ben-Dov IZ, Shapira Y, et al. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology*. 2006; 130: 1129-34.
- Feinstone SM, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. *Science* 1973; 182:1026.
- Hammit LL, Bulkow L, Hennessy TW et al. Persistence of antibody to hepatitis A virus 10 years after vaccination among children and adults. *J. Infect. Dis.* 2008: 198, 1776-1782.
- Hollinger FB and Ticehurst JR. Hepatitis A virus. In: Fields BN, Knipe DM, and Howley PM, editors. *Fields Virology*, 3rd ed. Philadelphia, Lippincott - Raven, 1996: 735-782.
- Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. *Vaccine* 1992;10 Suppl 1:S15-7.
- Lemon SM, Jansen RW, Brown EA. Genetic, antigenic and biological differences between strains of hepatitis A virus. *Vaccine* 1992; 10: S40-4.
- Lemon SM. Type A viral hepatitis. New developments in an old disease. *N Engl J Med.* 1985; 313: 1059-67.
- Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. *Am J Epidemiol* 1985; 122: 226-33.
- RKI (Robert Koch Institut, Germany): *Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2006*. 2006.
- Schiff ER. Atypical clinical manifestations of hepatitis A. *Vaccine* 1992; 10: S18-20.
- Tong MJ, Thursby M, Rakela J, McPeak C, Edwards VM, Mosley JW. Studies on the maternal-infant transmission of the viruses which cause acute hepatitis. *Gastroenterology* 1981; 80: 999-1004.
- Tong MJ, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. *J Infect Dis* 1995; 171: S15-8.
- Vento S, Garofano T, Di Perri G, Dolci L, Concia E, Bassetti D. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. *Lancet* 1991; 337: 1183-7.
- Vento S, Garofano T, Renzini C et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; 338: 286-90.
- Viral Hepatitis Prevention Board. News from the VHPB meeting in St. Julians, Malta. *Viral Hepatitis* 1997; 6: 6.
- Wasley A, Miller JT, Finelli L. Surveillance for acute viral hepatitis--United States, 2005. *MMWR Surveill Summ.* 2007; 56: 1-24.
- Wheeler C, Vogt TM, Armstrong GL et al. An outbreak of hepatitis A associated with green onions. *N Engl J Med* 2005; 353: 890-7.
- WHO (World Health Organization): *Hepatitis A*. World Health Organization. Department of Communicable Disease Surveillance and Response.
- Zhang RL, Zeng JS, Zhang HZ. Survey of 34 pregnant women with hepatitis A and their neonates. *Chin Med J (Engl)* 1990; 103: 552-5.