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病毒性肝炎

VIRAL HEPATITIS

EDITED BY
ARIE J. ZUCKERMAN
HOWARD C. THOMAS

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PREFACE

The editors are grateful to the chapter authors for updating and expanding their contributions to this second edition of *Viral Hepatitis.* The book is again aimed at filling the needs of clinicians, virologists, epidemiologists, and pathologists for an easily accessible and balanced reference source and as a starting point for research students entering the field.

The progress has been rapid. Not only have there been considerable advances in our knowledge of the existing viruses A to E, but we have several additions to the Flaviviridae family, GBV-A, GBV-B, and GBV-C (also known as HGV), which are now included.

To accommodate those clinicians, pathologists, and epidemiologists who have a ''problem-oriented'' rather than a ''virus-specific'' approach to the subject, we have included a series of topic chapters to help meet some of their needs. We hope, therefore, that this book will function as a meeting place for virologists and clinicians.

ARIE J. ZUCKERMAN
HOWARD C. THOMAS

CONTENTS

1

CLINICAL FEATURES OF HEPATITIS

S. Sherlock

There are many varieties of viral hepatitis.[83] Hepatitis A is a self-limited fecally spread disease. Hepatitis B is a parenterally transmitted disease that often becomes chronic. Hepatitis D is parenterally spread and affects only those with hepatitis B infection. Hepatitis C is a parenterally spread disease with a high chronicity rate. Hepatitis E and hepatitis G resemble hepatitis A. They are enterically spread, usually via water, and cause a self-limited hepatitis in underdeveloped countries. There will undoubtedly be other members of the hepatitis alphabet. General clinical features are common to all the virus infections. In general, types A, B, and C run the same clinical course. Types B and C tend to be more severe and may be associated with a serum sickness-like syndrome.

The mildest attack is without symptoms and marked only by a rise in serum transaminase levels. Alternatively, the patient may be anicteric but suffer gastrointestinal and influenza-like symptoms. Such patients are likely to remain undiagnosed unless there is a clear history of exposure, or the patient is being followed up after a blood transfusion. Increasing grades of severity are then encountered, ranging from the icteric, from which recovery is usual, to fulminant, fatal viral hepatitis.

The usual icteric attack in adults is marked by a prodromal period, usually about 3 or 4 days, but even up to 2 to 3 weeks, during which the patient feels generally unwell, suffers digestive symptoms, particularly anorexia and nausea, and may, in the later stages, have a mild pyrexia. Rigors are unusual. An ache develops in the right upper abdomen. This is increased by jolting movements. There is loss of desire to smoke or to drink alcohol. Malaise is profound and increases toward evening; the patient feels wretched. Occasionally, headache may be severe, and in children, its association with neck rigidity may suggest meningitis. Protein and lymphocytes in the cerebrospinal fluid (CSF) may be raised.

The prodromal period is followed by darkening of the urine and lightening of the feces. Symptoms decrease and jaundice develops. The temperature returns to normal and there may be bradycardia. Appetite returns and abdominal discomfort and vomiting cease. Pruritus may appear transiently for a few days.

The liver is palpable with a smooth tender edge in 70% of patients. Heavy percussion over the right lower ribs posteriorly causes sickening discomfort. The spleen is palpable in about 20% of patients.

The adult loses about 4 kg in weight. A few vascular spiders may appear transiently. After an icteric period of about 1 to 4 weeks, the adult patient usually makes an uninterrupted recovery. In children, improvement is particularly rapid, and jaundice is mild or absent. The stools regain their color. The appetite becomes normal. After apparent recovery, lassitude and fatigue persist for some weeks. Clinical and biochemical recovery is usual within 6 months of the onset. However, chronic hepatitis may follow types B, C, and G.

Neurological complications, including the Guillain-Barré syndrome, can complicate all forms of viral hepatitis. Occasionally, prolonged jaundice is of cholestatic type. Onset is acute; jaundice appears and deepens, but within 3 weeks the patient starts to itch. After the first few weeks, the patient feels well and gains weight, and there are no physical signs apart from icterus and slight hepatomegaly. Jaundice persists for 8 to 29 weeks, and recovery is then complete. This type must be differentiated from surgical obstructive jaundice.[35] The acute onset and only moderately enlarged liver are the most helpful points. Cholestatic drug jaundice is excluded by the history. Relapses occur in 1.8% to 15% of cases. In some, the original attack is duplicated usually in a milder form. More often, relapse is simply shown by an increase in serum transaminases and sometimes bilirubin. Multiple episodes may occur. Recovery after relapse is usually complete. In some, relapses may indicate progression to chronic hepatitis.

Fulminant viral hepatitis usually overwhelms the patient within 10 days. It may develop so rapidly that jaundice is inconspicuous, and the diagnosis is confused with an acute psychosis or meningoencephalitis. Alternatively, the patient, after a typical acute onset, becomes deeply jaundiced. Ominous signs are repeated vomiting, fetor hepaticus, confusion, and drowsiness. The flapping tremor may be only transient, but rigidity is usual. Coma supervenes rapidly, and the picture becomes that of acute

liver failure. Temperature rises, jaundice deepens, and the liver shrinks. Widespread hemorrhage may develop.

HEPATITIS A HEPATITIS

Hepatitis A virus (HAV) hepatitis occurs sporadically or in epidemic form and has an incubation time of 15 to 50 days (Fig. 1-1). It is usually spread by the fecal–oral route. Parenteral transmission is extremely rare, but can follow transfusion of blood from a donor who is in the incubation stage of the disease.[43]

Age 5 to 14 is the group most affected, and adults are often infected by spread from children as a result of overcrowding, poor hygiene, and poor sanitation. With improved standards of living, the prevalence is decreasing worldwide. In urban areas, only about 30% of adults show IgG anti-HAV, whereas in underdeveloped countries, 90% of children have the antibody by the age of 10. Young people, not previously exposed, and visiting endemic areas, are increasingly becoming affected. Medical staff in developed countries are at risk. A large outbreak among nurses and mothers in a nursery spread from an acute HAV in the neonate with an ileostomy.[9] In another outbreak, two infants in a neonatal intensive care unit received blood from an HAV-infected donor.[80] This resulted in infection in 13 infants, 22 nurses, 8 other staff caring for the infants, and 4 household contacts. The infants excreted virus for 4 to 5 months after they were infected.

Outbreaks have been reported among hemophiliacs receiving solvent-detergent treated factor VIII concentrates and were presumably due to infection of plasma by blood donors who were incubating hepatitis A.[63] Most sporadic cases follow person-to-person contact. Children in day care centers and promiscuous homosexual men are at risk.

Clinically, the hepatitis is usually mild, particularly in children, in whom it is frequently subclinical or passed off as gastroenteritis. The disease is more serious and prolonged in adults.

The nephrotic syndrome has been reported with immune complex-mesangial, proliferative glomerulonephritis.[99]

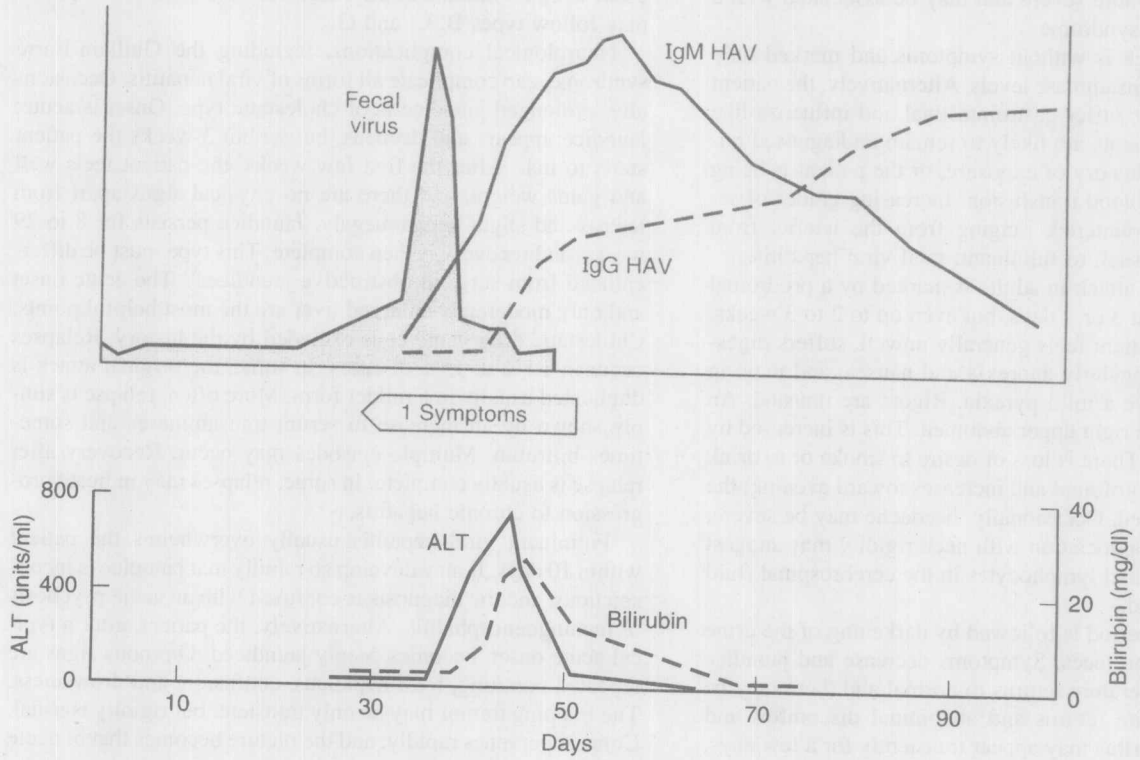
Cholestatic Hepatitis A

This form of hepatitis A affects adults.[35] The jaundice lasts 1 to 4 months and itching is severe. Serum IgM anti-HAV is positive. The prognosis is excellent.

Relapsing Hepatitis A

Occasionally after 30 to 90 days, the patient suffers a relapse. The serum transaminase levels have never returned to normal. The disease resembles the original attack clinically and biochemically, and virus A is found in the stools.[84] The relapse may last several months, but recovery eventually ensues. A report from Israel described 14 well-documented cases of relapsing HAV infection[34] (Fig. 1-2). They have been confirmed by positive-serum IgM anti-HAV tests. One or more relapses followed initial resolution of the clinical manifestations. This

Figure 1-1. The course of acute hepatitis A. ALT, alanine aminotransferase; HAV, hepatitis A virus.



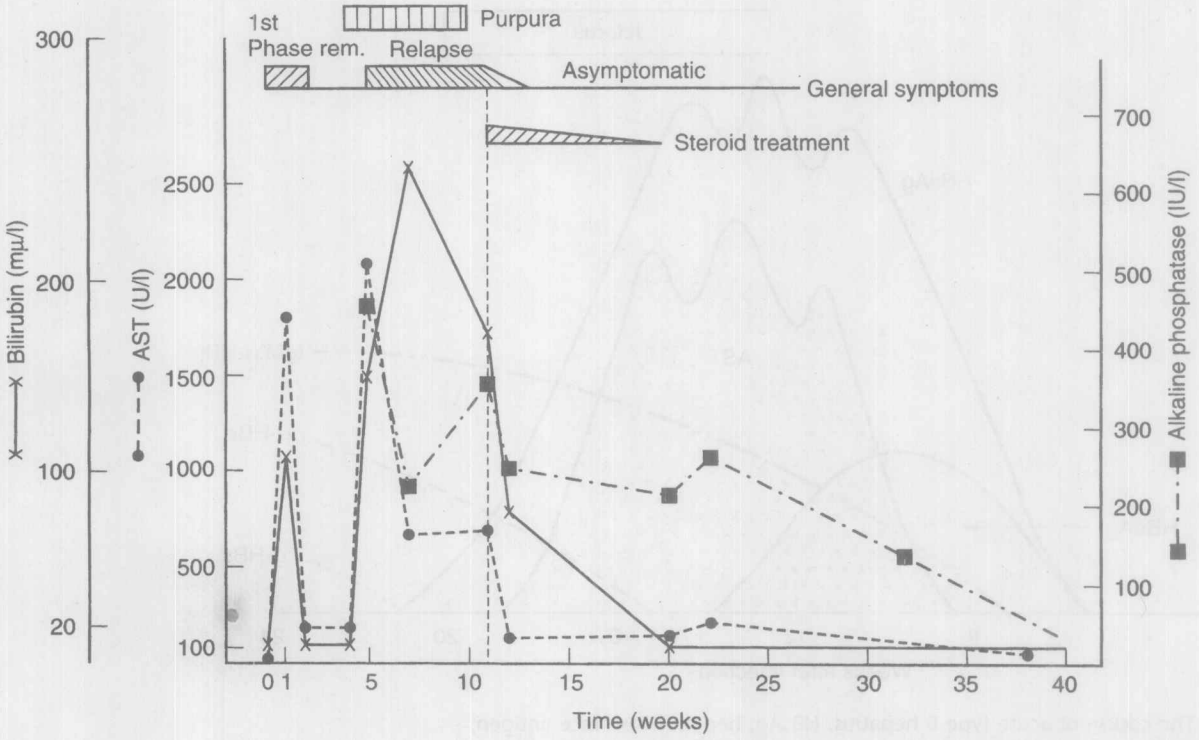


Figure 1-2. Clinical and biochemical course of a patient with relapsing hepatitis A. Rem, remission; AST, aspartate transaminase. (From Glikson et al,[34] with permission.)

relapsing form may affect 3.8% to 20% of patients with an initial episode of acute HAV infection. Relapsing HAV is associated with continuing viremia and shedding virus in stools during the relapse phase.[84] The pathogenesis probably involves an interaction between persistent viral infection and immune mechanisms responding to the continuing antigenic stimulation. Rarely, the relapse can be associated with arthritis, vasculitis, and cryoglobulinemia.[21]

HEPATITIS B VIRUS

Hepatitis B virus (HBV) is transmitted parenterally or by intimate, often sexual, contact. The incubation period is about 6 weeks (Fig. 1-3).

The carrier rate of hepatitis B surface antigen (HBsAg) varies worldwide from 0.1% to 0.2% in Britain, United States, and Scandinavia to more than 3% in Greece and Southern Italy, and even up to 10% to 15% in Africa and the Far East. Carriage of HBsAg is even higher in some isolated communities such as Alaskan Eskimos and Australian Aborigines.

In high-carriage rate areas, infection is acquired by passage from the mother to the baby. The infection is usually not via the umbilical vein, but from the mother at the time of birth and during close contact afterward. The risk of transmission increases as term approaches and is greater in acute than in chronic carriers. The mother is HBsAg-positive, and also, but not always, hepatitis Be antigen (HBeAg)-positive. Antigenemia develops in the baby within 2 months of birth and tends to persist.[13] There is an inverse relationship between the risk of chronicity and the age of infection, the risks being 80% to 90% for infections before the age of 1 year, and 20% to 50% for infections in early childhood.[18] In contrast, hepatitis B infection in adults gives rise to a carrier rate of only 1% to 2%.[81,86]

In high endemic areas such as Africa, Greece, and Hong Kong, the transmission is in childhood and is probably horizontal[19] through kissing and shared utensils such as toothbrushes and razors. Contact in preschool day care centers is possible. Sexual contacts in the family are at risk.[6]

Infection is frequent in homosexuals and is related to duration of homosexual activity, number of sexual contacts, and anal contact.

Blood transfusion continues to cause hepatitis B in countries where donor blood is not screened for HBsAg. Transmission is more likely with blood from paid donors than from volunteer blood.

Opportunities for parenteral infection include the use of unsterile instruments for dental treatment, ear piercing and manicures, neurological examination, prophylatic inoculations, subcutaneous injections, acupuncture, and tattooing.

Parenteral drug abusers develop hepatitis from using shared, unsterile equipment. The mortality rate may be high in this group.

Hospital staff in contact with patients, and especially patients' blood, usually have a higher carrier rate than the general community. This applies particularly to staff on renal dialysis or oncology units. The patient's attendant is infected through contact with blood parenterally such as from pricking or through skin abrasions. Surgeons and dentists are particularly at risk in