Hepatitis A

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There are exciting new developments in the serology of hepatitis A. These new studies will lead to the development of diagnostic tests comparable to the Australia antigen (HB_sAg) for hepatitis B. Although active immunization is not likely to be available in the near future, passive immunization is effective. Most patients with clinical disease will recover uneventfully with good diet and ad lib activity. Severe restrictions and hospitalization are rarely indicated.

"Infectious hepatitis" was described by Hippocrates more than 2,000 years ago. However, its viral etiology was not discerned until 30 years ago when hepatitis was produced by passage of a filterable agent in human transmission experiments. These agents were shown to be relatively resistant to heat and to chemical disinfectants.

In their studies at the Willowbrook State School, Staten Island, Krugman and Giles showed that there were two immunologically distinct types of viral hepatitis.[1] Their MS-1 strain (patient-M, serum-S, 1-1st attack) was shown to have a short incubation period (15 to 40 days) and to be transmitted by the "fecal-oral" route most commonly. Their MS-2 strain had a longer incubation period of 40 to 180 days and was thought to be transmitted totally by the parenteral route.

MS-1 was shown to be identical to hepatitis A,[2] and was shown to confer resistance to hepatitis A infection but not to hepatitis B. This was done by rechallenging a patient after recovery from hepatitis A with MS-1 virus, failing to produce illness, but producing clinical hepatitis B with MS-2 strain after complete recovery from hepatitis A. Krugman and associates also showed that hepatitis B was infectious by the oral route.[1]

Study of the virus was thwarted for years by inability to reproduce the illness in an animal model. It was in 1966 that Deinhart and Holmes were able to transmit hepatitis A to the marmoset, a small primate,[3] and in 1974 that Purcell at the National Institutes of Health transmitted hepatitis to chimpanzees. These experimental advances followed the observation of development of typical hepatitis A in animal handlers caring for chimpanzees newly arrived in this country.

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Serologic Testing for Hepatitis A

In 1973 Hilleman showed that convalescent human serum could neutralize the virus of hepatitis A making it non-infectious in monkeys.

Also in 1973, the first electron-microscopy photographs of virus A in the stool of patients with hepatitis A were made by the addition of convalescent serum to stool extract which produced clumping of 27 nm particles. Control serum failed to produce this clumping. These particles were then used to produce hepatitis in chimpanzees and marmosets and have now been shown to be an enterovirus with a ribonuclease core.

Using the "hepatitis A particle" in hepatic extract from marmosets with hepatitis, convalescent serum, guinea pig complement, and Group O red blood cells. Miller et al have produced an immune adherence test capable of distinguishing with accuracy the presence in serum of antibody to hepatitis A.[4]

Krugman, Friedman, and Lattimer

in 1975 reported on their studies in which frozen serum specimens collected since 1956 on all admissions to the Willowbrook State School (before exposure to hepatitis, during the incubation period [after exposure], during the acute and convalescent phases of the disease, and serially for years thereafter), were tested by the immune adherence method using Ag extracted from liver of marmosets infected with hepatitis A virus (CR 326).[5] They demonstrated no antibody in pre-exposure serum. At one to four weeks after onset of hepatitis A (within two weeks in 80 percent), antibody was detectable in titres of 1:5,120 to 1:327,680. At five and ten-year follow-up antibody was still detectable at 1:640 to 1:20,480. No antibody was detected in patients who had hepatitis B only (MS-2).

These studies are the first breakthrough in the development of easily applied serologic tests for the detection of hepatitis A.

Epidemiology

Most commonly hepatitis A outbreaks have been attributed to transmission via the fecal-oral route, usually in situations of poor sanitation, crowding, and among institutionalized elderly or mentally retarded patients after exposure of non-immune population.

In a study presented in June 1976, 12 cases of hepatitis A developed in families into which Vietnamese children had been adopted through a single Colorado adoption agency.[6] The incubation period was 18-49 days and all cases were HAA negative. All 12 cases occurred in members of the American family and none of the Vietnamese children were clinically ill, although 27 percent were HB_sAg positive and 30 percent were anti-HB_sAg positive.

In 1974, Meyers et al documented parenteral transmission of hepatitis A.[7] They reported the occurrence of hepatitis A in a leukemia research center in nine patients with marrow transplants and six platelet-plasma donors over a three-month span. There were an additional 21 subclinical cases (↑SGOT). The attack rate was 90 percent among donors and 69 percent in platelet recipients. The incubation period was 27 days and all were HAA negative and had negative serology for cytomegalovirus, Q fever, and infectious mononucleosis. A break in plasmapheresis technique was felt to be responsible for the outbreak.

Food-borne outbreaks are not frequently reported, but since 1950 there are 12 documented food-borne outbreaks in the literature occurring in school (1), college (1), community (5), picnic (1), naval barracks (1), army camp (1), a general hospital (2), and a department store (1). The vehicles have varied from green salads to roast pork. The hospital outbreaks were traced to orange juice in one instance and to sandwiches served in the visitors' lounge in another.[8-10]

Water-borne outbreaks have been documented in the Holy Cross football team in 1972 (related to drinking water, 90 percent attack rate),[11] and in cross-country runners due to contamination of superficial scratches. The runners had crossed through contaminated streams after being scratched by bushes.

Other vehicles reported have been raw milk, inadequately cooked shellfish, and exposure to newly imported primates with inapparent disease.

Pathology

Typical pathological changes consist of parenchymal cell degeneration and necrosis, proliferation of Kupffer's cells, and inflammatory cell infiltration. The necrosis is usually patchy and centrilobular with disrupted cords, but there is preservation of the fibrous stroma. There may be ballooning of the cytoplasm or hyalinization of cells with pyknotic nuclei.

If there is the clinical picture of intrahepatic obstruction, there will be bile duct proliferation and bile plugging of the canaliculi. Cell regeneration with numerous mitoses, and large cells with multiple hyperchromatic nuclei characterize the recovery phase.

There may be edema and mononuclear cell infiltration of the gut mucosa and renal histology may demonstrate interstitial edema without cellular infiltration.

Clinical

Hepatitis A ranges in clinical effect from a mild, anicteric to a fulminant process (<1 percent). The illness may be divided into several stages.[2]

Prodromal Stage

In hepatitis A this stage is usually abrupt in onset and lasts 3 to 14 days, during which time there is *viremia.* Symptoms are fatigue, malaise, headache, fever (usually mild, but may be severe with shaking chill at onset – recurrent chills are unusual), nausea and vomiting, and loss of taste for cigarettes (thought by many to be due to anosmia due to effect of illness on olfactory bulb). Skin rash (usually urticarial), joint pain, and thrombophlebitis are more common in hepatitis B. During this period there may be mild increase in hepatic size and right upper quadrant tenderness. There is usually bilirubinuria at this point.

Icteric Stage

Symptoms during this time may be a continuation or worsening of those of the prodromal phase. These usually consist of anorexia, nausea and vomiting, right upper quadrant discomfort, and hepatic enlargement and tenderness. The spleen may or may not be enlarged. Fever usually decreases with the onset of jaundice. Peak of jaundice usually occurs at 7 to 14 days and is not clinically evident at one month in approximately 60 percent of the patients and has resolved at three months in 90 percent of the patients. There

may be transient rises in bilirubin after this time associated with vigorous activity or use of alcohol. Diuresis usually heralds the onset of improvement. Patients with G-6-P-D deficiency may develop hemolysis causing marked increased in bilirubin which may confuse the clinical picture,[12] although the bilirubin fraction is predominantly the unconjugated fraction.

Cholestatic Jaundice

This is the name given to the clinical syndrome of prolonged, severe jaundice accompanied by pruritis (the result of bile salt retention). The liver remains enlarged during the entire period of jaundice. There may be rather marked diarrhea as a result of nonabsorbed fatty acids. In prolonged cholestasis, care should be taken to replace fat-soluble vitamins parenterally.

Convalescent Stage

This phase may last weeks to months and may be characterized by fatigue, malaise, and mild hepatic tenderness, often related to activity. The protracted course may be quite bothersome to the patient and requires close follow-up and frequent reassurance that the patient is not relapsing.

Laboratory Guides

Liver function tests may present a pattern helpful in distinguishing viral hepatitis from other hepatobiliary disorders, but may often be misleading. Laboratory data may, however, provide specific diagnostic information for ruling out infectious mononucleosis, syphilis, leptospirosis, cytomegalovirus, Q fever, etc. Such data can also be of value in deciding on the safety of liver biopsy.[13]

SGOT is found in liver, heart muscle, skeletal muscle, kidney, and pancreas. Increased levels are an early feature of hepatitis and may precede jaundice by two weeks. Levels also rise in anicteric hepatitis. Typically GOT & GPT fall rapidly after onset of jaundice and may return to normal while the serum bilirubin is still elevated. Level of GOT cannot be used as an index of severity of disease since levels may fall even in fulminant hepatitis.

SGPT – The only organ where there are substantial levels of GPT is liver; therefore, it is fairly specific for liver disease.

Krugman found "spiking" rise in SGOT in hepatitis A with total duration of elevated serum levels rarely longer than three weeks.[2] He found a more gradual rise in hepatitis B and a much slower fall (several months). The SGPT stays abnormal longer, even in hepatitis A (Holy Cross outbreak).[11]

The OT/PT ratio is not of value in differentiating viral from other types of hepatitis. This original concept of such differentiation is based on the fact that SGOT is present in both cytoplasm and mitochondria, whereas SGPT is found only in the cytoplasm. Therefore, with mild, reversible hepatocellular damage there would be a measurable increase in cytoplasmic enzymes only, whereas with severe hepatocellular damage there would be release of mitochondrial enzymes. This has not proven to be clinically useful.

Bilirubin – Levels are increased with increase in direct (conjugated) fraction. Urinary bilirubin levels rise early and brown urine may precede the onset of jaundice. In hemolysis and Gilbert's disease, the increase is in the unconjugated fraction.

Alkaline phosphatase – There are five isoenzymes including hepatic and biliary components. Usually serum levels are mildly increased in viral hepatitis, but in cholestatic hepatitis the levels may be very high.

5′ nucleotidase – The rise in serum levels parallels the rise in the hepatic isoenzymes of alkaline phosphatase. They also rise in pregnancy along with the rise in placental alkaline phosphatase.

Albumin – Serum albumin levels are of little value in the usual case of viral hepatitis because the plasma half-life is 20 days and levels remain normal in most patients.

Miscellaneous – Increased B_{12} levels may result as B_{12} is released from damaged hepatocytes. Serum iron is elevated in 50-80 percent of patients with viral hepatitis. There is usually a non-specific rise in gamma globulin in infection. IgM levels may be elevated in the first week, then decrease in convalescence. Thymol turbidity was higher in MS-1 (hepatitis A) than in MS-2 hepatitis in Krugman's study.[1] Alpha-1-fetoprotein has been found to be present in low levels in hepatitis A, but not in hepatitis B.

Coagulation tests – The prothrombin time shows better correlation than serum enzymes and bilirubin with overall severity of the illness. It depends on normal amounts of factors I, II, V, VII, and X. It is also useful when the question of biopsy is raised.

Serum cholesterol – This may greatly increase in cholestatic hepatitis and remain low in severe attacks of hepatitis without obstruction. Falling cholesterol levels suggest a poor prognosis.

Hematologic profile – Target cells on the peripheral film are not unusual. This is related to increased lipid content of the red blood cell membrane. Patients have been described with aplastic anemia, severe hemolytic anemia, agranulocytosis, thrombocytopenia, and pancytopenia.

Urine – Proteinuria, red blood cells, and red blood cell casts have been found. Immune complex nephritis has been described with hepatitis B, but not with hepatitis A. Pyuria without bacilluria may be found.

Management

Hospitalization is indicated for patients with severe symptoms or signs of massive necrosis (bleeding, edema, ascites, encephalopathy), and for high-risk patients, ie, pregnant, diabetic, elderly, and patients who are immunosuppressed. Bed rest should be ad lib for the young and otherwise healthy but should probably be enforced for the high-risk patient especially during the early symptomatic period if the patient is icteric.

Diet should be at least 2,000 Cal per day. Protein should not be restricted except where encephalopathy is a problem.

Prophylaxis (See Appendix.)

There is currently no method of active immunization against hepatitis A.[14] Destroying the virus infectivity also destroys its antigenicity. Future developments in this area are, however, anticipated.

Appendix.[14] Prophylaxis of Hepatitis A

Hepatitis A — Incubation period 15-50 days ($\bar{x}$ 25-30)

Stools infective 2-3 weeks prior to 2 weeks after onset of jaundice.
Blood is infective 2 weeks before but less than 1 week after onset of jaundice.
Parenteral transmission possible.

Immune Serum Globulin — 16.5% protein obtained by cold ETOH fractionation of large plasma pools. Has Ab vs diphtheria, measles, polio. Neither hepatitis-A nor hepatitis-B ever transmitted by ISG.

Specific Recommendation for Hepatitis-A

1. If given before exposure or during incubation period, it offers 80-90% protection.
2. Long-lasting natural immunity may result (failure of ISG to affect inapparent infection).
3. Prophylactic value greatest when given early and decreases with time after exposure.
4. Do not give greater than six weeks after exposure *or* after onset of clinical illness.

Dosage

Approximately 0.01 cc/lb or 0.02 cc/kg body weight.

Guide:
<50 lb — 0.5 cc
50-100 lb — 1.0 cc
>100 lb — 2.0 cc

Household Contacts

All who have never had hepatitis-A should receive ISG.

School

Routine administration to teacher and pupil contacts *not* indicated.

Classroom centered outbreak — administer ISG.

Institutional (Prisons, homes for mentally retarded) — can limit spread of disease. Where endemic, give 0.02-0.05 cc/lb at time of admission or employment and repeat every six months (not recommended for endemic hepatitis-B).

Hospital Workers

Not routinely done.

Hemodialysis

Not routine.

Common Source

(Food, water, etc) — administer ISG.

Travelers

>3 months in tropical or developing countries.
Guide:
<50 lb — 1.0 cc
50-100 lb — 2.5 cc
>100 lb — 5.0 cc
Repeat every 4-6 months.

Pregnancy

Not a contraindiction to ISG.

ISG *may* be protective against hepatitis-B when transmission is non-parenteral.

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