Clinical Manifestations of Hepatitis A: Recent Experience in a Community Teaching Hospital

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A study of the clinical profile of 59 patients who presented with hepatitis A virus infection showed that dark urine, fatigue, gastrointestinal complaints, and fever were the most common presenting symptoms. The most frequent physical findings were hepatomegaly and jaundice. The mean presenting laboratory tests included total bilirubin of 5 mg/dL, alkaline phosphatase of 269 units/L, and serum aspartate aminotransferase and alanine aminotransferase levels of 1442 mlU/mL and 1952 mlU/mL, respectively. Atypical manifestations included relapse, cholestasis, rash, and arthralgia. Two patients presented with hepatitis A and concomitant type I autoimmune chronic hepatitis, and both required immunosuppressive therapy. Five patients who presented with hepatitis A were pregnant, and during follow-up, none of their infants developed elevated serum transaminase values or had detectable IgM anti-HAV antibody. All 59 patients experienced complete clinical and biochemical recovery within 6 months after onset of illness.

Acute hepatitis A is a common viral infection found throughout the world and is spread principally via the oral-fecal route. In the United States, hepatitis A accounts for ~20% of the cases of viral hepatitis reported annually to the Centers for Disease Control and Prevention [1].

The clinical spectrum of acute hepatitis A virus (HAV) infection is varied and includes silent infection detected only by viral serologic testing, subclinical infection revealed by abnormal liver tests, clinically apparent hepatitis, and, rarely, fulminant hepatitis, which is associated with coma and occasionally death. While most infants and children have silent or subclinical infections, the majority of adults develop symptoms and signs of acute disease. Atypical manifestations such as relapse, cholestasis, rash, and arthralgia also have been described in patients with hepatitis A, but the pathophysiology of these phenomena has not been elucidated.

For discussion of the clinical aspects of acute HAV infection beyond the scope of this report, there are several excellent reviews [2-4]. Here we present the clinical manifestations of 59 patients with acute hepatitis A who were recently referred to a liver center at a community teaching hospital.

Materials and Methods

Patients who were referred to the Liver Center, Huntington Memorial Hospital, with symptoms and signs of acute hepatitis were screened for hepatitis A by testing their sera for IgM anti-HAV antibody (HAVAB-M; Abbott, Abbott Park, IL). Patients who tested positive were considered to have HAV infection and were followed every 2-4 weeks until complete recovery. At each clinic visit, a complete blood cell count and tests for serum bilirubin, ALT, and AST were done.

Medical records for patients with HAV infection were retrospectively reviewed for symptoms, signs, and laboratory values including bilirubin. ALT, and AST. Complete recovery from hepatitis A was defined as resolution of all clinical symptoms and normalization of liver tests. A relapse was defined as a biphasic or second peak of serum ALT elevation after complete or partial resolution of the first transaminase peak. The cholestatic phase of hepatitis A was defined as a persistent elevation in serum bilirubin of >3 mg/dL for >3 months after onset of illness. The presence of coexisting hepatitis A and chronic autoimmune hepatitis was confirmed by the presence of both IgM anti-HAV and autoantibodies (anti-nuclear antibody or smooth muscle antibody) along with liver biopsy findings consistent with type I autoimmune chronic hepatitis. Infants born to mothers with acute hepatitis A were followed every 1 or 2 months after birth and tested for serum ALT and IgM anti-HAV.

Results

Clinical Features

Patients. During the past 10 years, 59 patients with acute hepatitis A were referred to the Liver Center at Huntington Memorial Hospital. Their average age was 29 years (range, 6-66), and the majority were 20-35. The ratio of male to female patients was about equal (29:30), and 80% were white. The probable exposures to HAV reported included household or sexual contact (47%), travel outside the United States (15%), and association with food- or waterborne sources (19%). Five patients who had a history of sexual contact with other hepatitis A patients included 2 heterosexual and 3 homosexual men. Three patients were intravenous
drug users. For the 11 patients who did not give an identifiable risk factor, there was a history of either recent tattooing, treatment with acupuncture needles, exposure to blood-contaminated equipment during manicure, or needlestick exposure in a health care setting.

**Signs and symptoms.** The main symptoms reported by the 59 patients with hepatitis A included dark urine (81%), fatigue (80%), gastrointestinal problems including anorexia, nausea, vomiting, and abdominal pain (75% to 41%), and fever (58%). Less common complaints were myalgia (32%), pruritus (29%), chills (27%), diarrhea (24%), headache (22%), arthralgia (19%), sore throat (7%), and rash (7%). Hyposmia, insomnia, and aversion to cigarette smoke were reported by a few patients. Hepatomegaly (78%) and jaundice (71%) were the most common presenting signs, with splenomegaly and cervical lymphadenopathy detected in only 7% and 4% of patients, respectively.

**Laboratory tests.** The mean presenting laboratory tests from 59 hepatitis A patients included total bilirubin of 5 mg/dL (mean peak, 7 mg/dL), alkaline phosphatase of 269 units/L (mean peak, 319 units/L), serum AST of 1442 mIU/mL (mean peak, 1754 mIU/mL), and ALT of 1952 mIU/mL. Atypical lymphocytes were noted in 7% of the patients. Three patients had bilirubin levels of >20 mg/dL (highest, 38 mg/dL). 2 patients had serum AST values of >5000 mIU/mL (highest, 9987 mIU/mL), and 6 patients had serum ALT levels of >5000 mIU/mL (highest, 9711 mIU/mL). Linear regression analysis of peak total bilirubin versus age indicated that bilirubin levels during acute hepatitis A increased with advancing age ($P < 0.001$). Bilirubin levels returned to nearly normal by a mean of 5.3 weeks (range, 0.5-33.0), alkaline phosphatase became normal by a mean of 5.3 weeks (range, 1-14), and serum AST and ALT values reverted to normal by a mean of 6.2 weeks (range, 0.5-29.0) and 7.4 weeks (range, 1-29), respectively.

**Recovery.** About two-thirds of our patients recovered within 2 months from onset of illness. Eighty-five percent were symptom-free with normal liver tests by 3 months, and nearly all were normal by 6 months. Only supportive treatment (diet, bed rest) was recommended during the course of the acute illness.

**Atypical Manifestations**

**Relapse.** Seven (11.9%) of the 59 patients in our study had a relapse of acute hepatitis A, which was characterized by a biphasic peak of serum transaminase elevation. After an initial peak and fall in serum transaminase levels, a second peak was noted 4-7 weeks after the first peak and was accompanied by the reappearance of clinical symptoms. Only 1 of the 7 patients had normal serum transaminase values during the first remission. The mean serum ALT and AST levels during the first peak were 3500 mIU/mL (range, 594-9771) and 2475 mIU/mL (range, 497-3654), respectively; during the second peak they were 1554 mIU/mL (range, 353-3654) and 1089 mIU/mL (range, 310-1708), respectively. The mean bilirubin level during the first serum ALT peak was 4.9 mg/dL (range, 2.5-7.1) and during the second ALT peak was 2.5 mg/dL (range, 0.6-4.8). Figure 1 shows the clinical course of a hepatitis A patient with relapse.

**Cholestasis.** A cholestatic phase of hepatitis A with persistently elevated bilirubin levels was noted in 4 (7%) of the patients. Their peak bilirubin levels ranged from 8 to 38 mg/dL (mean, 20), and the duration of elevation was 12-16 weeks (mean, 14) after the onset of symptoms. During the cholestatic phase, serum AST and ALT levels normalized by 14 weeks after onset. Pruritus, fatigue, loose stools, dark urine, and weight loss accompanied the prolonged cholestasis. Figure 2 shows the clinical course of a patient with hepatitis A who had cholestasis.

**Rash and arthralgia.** Only 7% of our patients had rash and 19% arthralgia. These symptoms were present during the prodromal phase of HAV infection.

**Type I autoimmune chronic hepatitis.** Two patients (3%) presented with signs and symptoms of acute hepatitis and positive IgM anti-HAV antibody tests and also had concomitant chronic autoimmune hepatitis. One woman and her husband had consumed shellfish during a visit to the East Coast of the United States, and both developed acute hepatitis. The source of infection in the second woman was her husband, who had contracted hepatitis A. On presentation, both had firm and grossly enlarged livers. Liver biopsy findings were consistent with chronic active hepatitis. One patient had a positive anti-nuclear antibody test, and the other had a positive smooth muscle antibody test. Both patients
received prednisone therapy with resolution of their chronic active hepatitis.

Other associated conditions. One hepatitis B carrier with chronic active hepatitis contracted acute HAV infection and had a prolonged course of illness. Finally, 2 patients experienced a post-viral hepatitis-like syndrome characterized by continual fatigue, right upper quadrant pain, and loss of appetite 6 months after laboratory tests indicated resolution of HAV infection. During this time, no other cause for these symptoms was detected.

Pregnancy. Five of our hepatitis A patients were pregnant: 1 each in the first and second trimester and 3 in the last trimester of pregnancy. After delivery, none of their infants had elevated liver tests or detectable IgM anti-HAV during follow-up.

Discussion

The symptoms and signs of acute hepatitis are protean and generally are not useful for distinguishing the different hepatitis viruses. However, for hepatitis A, the presence of fever and diarrhea during the prodromal period may lead the physician to suspect HAV as the etiologic agent. In our 59 hepatitis A patients, fever was present in 58% and diarrhea in 24% of cases. These findings were similar to those reported in reviews [2-4] in which fever was noted in 18%-75% and diarrhea in 16%-25% of patients. In our hepatitis A patients, hepatomegaly (78%) and jaundice (71%) were frequently detected, while 7% had splenomegaly. The mean presenting bilirubin, AST, and ALT levels in our hepatitis A patients were similar to those in other reports [2-4]. However, 1 of our patients had peak serum ALT and AST values of 9987 and 9711 mIU/mL, respectively. In general, the high transaminase levels did not appear to influence the rate of recovery. However, patients with high bilirubin levels, especially those with prolonged cholestasis, had a protracted clinical course. Also, the peak bilirubin levels observed in our hepatitis A patients appeared to increase with advancing age.

The most common atypical manifestation noted in our hepatitis A patients was a relapsing course characterized by two peaks of serum transaminase elevation. In these patients, the mean serum bilirubin, AST, and ALT levels were higher during the first than during the second peak. Other investigators have shown that HAV was detected in the stools and HAV RNA was present in the serum of patients not only during the incubation period of hepatitis A but also during
the relapsing phase [5, 6]. The frequency of this biphasic or relapsing form of hepatitis A noted in our patients (12%) was similar to that reported [7]. However, its pathogenesis remains to be elucidated.

Four of our patients with hepatitis A had a prolonged cholestatic phase in which elevated bilirubin was present for up to 16 weeks after the onset of acute illness. During this time, mean peak bilirubin levels of 20 mg/dL (highest, 38 mg/dL) were noted even in the presence of declining AST and ALT levels. In patients with cholestasis, clinical symptoms persisted throughout the course of illness, with pruritus and fatigue as the predominant complaints. Liver biopsies obtained from patients during the cholestatic phase of hepatitis A showed marked centrilobular cholestasis and portal inflammation resembling chronic hepatitis [8].

Of our patients with acute hepatitis A, 19% noted a skin rash and 1% complained of arthralgia. These clinical findings also have been observed in some patients with acute hepatitis B, in association with circulating immune complexes and complement activation [9]. In hepatitis A, skin biopsy findings obtained from patients with vasculitic changes and arthritis during the cholestatic or relapsing phase showed leukocytoclastic vasculitis with deposition of IgM and C3 in the blood vessel wall and circulating cryoglobulins that contained IgM anti-HAV and polyclonal IgM and IgG [10-12].

Two patients (both women) presented with acute hepatitis A and also had findings of chronic autoimmune hepatitis. A recent report indicated that HAV may trigger autoimmune chronic hepatitis [13]. However, it is unclear whether our 2 patients had underlying chronic active hepatitis with coincidental exposure to hepatitis A or whether HAV acted as a trigger for autoimmune hepatitis.

Five patients who presented with acute hepatitis A also were pregnant. When their infants were followed for up to 6 months after delivery, none had elevated serum transaminase values or developed IgM anti-HAV antibody. We previously reported that HAV did not appear to be transmitted from infected mothers to their newborn infants [14]. This may be because hepatitis A is transmitted via the oral-fecal route, and fecal contamination from mother to newborn usually does not take place during delivery. In addition, IgG anti-HAV antibody is invariably present during the initial stages of HAV infection, and these antibodies will cross the placenta and provide protection to the infant after delivery.

The recovery rates for our patients were similar to those reported in the literature for adults with symptomatic acute hepatitis A. Almost two-thirds recovered within 2 months, 85% by 3 months, and nearly all by 6 months [2]. In general, the clinical outcome for HAV infection is excellent. All patients, except for the few who die of fulminant hepatitis (<1%), fully recover. There is no specific treatment for acute HAV infection. Antiviral intervention is unwarranted since clinical recovery is complete and a chronic HAV carrier state does not exist. Although bed rest during the height of illness may alleviate fatigue, it may not alter the natural course of recovery. Patients are encouraged to maintain adequate nutritional intake. Administration of prednisone was reported to improve clinical symptoms and hasten recovery during the cholestatic phase of the infection [7]. Referral to a liver transplant center is appropriate for patients with fulminant hepatitis A.

References