Risk of hepatitis A superinfection in patients with underlying liver disease

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Abstract

During recent years the outcome of acute hepatitis A in chronic liver disease has been discussed controversially. Data from large hepatitis A epidemics and surveillance data from the United States suggest a significantly higher risk of fatal outcome in patients with chronic hepatitis B. Patients with chronic active hepatitis or liver cirrhosis seem to be at highest risk, while HBsAg carriers may exhibit a benign course of the disease. Patients with chronic hepatitis C also seem to have a significantly higher risk of fulminant hepatic failure when superinfected with hepatitis A. The recently reported unsuspected coincidence of autoimmune markers with a fulminant course of hepatitis A in those patients needs to be confirmed. Vaccination against hepatitis A in patients with chronic liver disease has been shown to be safe and effective. (Acta gastroenterol. belg., **1998**, 61, **206-209**).

Key words : hepatitis A infection, chronic liver disease, superinfection, risk of, hepatitis B infection, HBsAg carrier, liver cirrhosis, HAV, HBV.

Introduction

The risk of fatal outcome of acute hepatitis A superimposed on chronic liver disease has been discussed controversially during recent years. Most studies investigated the outcome of hepatitis A superinfection in patients with chronic hepatitis B. Recently, a first study of patients with chronic hepatitis C was published suggesting an increased risk for severe liver disease and fulminant hepatic failure. Comprehensive data on the outcome of hepatitis A superinfection in patients with preexisting liver disease are needed to assess the role for prevention strategies by hepatitis A vaccination.

Patients with hepatitis B

Large outbreaks of hepatitis A in East Asia have provided information on this topic. An epidemic related to the consumption of raw clams in Shanghai resulted in 310.746 cases of acute hepatitis A in 1988. 91% of the patients were young adults beween 20 and 40 yr of age (1), 8647 patients were hospitalized, and most presented with cholestatic hepatitis. HBsAg was detected in 8.8% of hospitalised cases corresponding to a similar HBsAg carrier rate in this region of China. Forty-seven patients died. The case fatality rate was 0.015%. 25/47 patients died of fulminant hepatitis A, 7/47 had other nonhepatic chronic diseases and 15/47 died of acute hepatitis A superimposed on chronic hepatitis B virus infection (11 HBeAg positive, 4 HBeAg negative). The histology of 5 hepatitis B patients who died was available. Three had submassive hepatic necrosis with cirrhosis, one had submassive hepatic necrosis with chronic active hepatitis and one subacute hepatic necrosis. Assuming a carrier rate of 8.8% for HBV infection, then 27,346 of the 310,746 HAV infected patients should have been HBsAg carriers. The case fatality rate for acute hepatitis A can then be calculated as 0.05% (15 deaths/27,346 patients) in HBsAg positive patients compared to 0.009% in HBsAg negative subjects (25 deaths/283,400 patients), thus resultinging in a 5.6 times higher case fatality rate in the subset of HBsAg positive patients (2). Data from the Centers for Disease Control reported 381 deaths in 115,551 patients with hepatitis A in the United States between 1983 and 1988, resulting in an overall case fatality rate of 0.3% (3). However, subdivision into age groups revealed a very low case fatality rate in the 5-14 year group (0.004%) compared to a 2.7% fatality rate in patients older than 49 yr. 70% of all deaths occurred in this age group, representing only 23% of the overall infections with hepatitis A. Twenty seven (7%) of the 381 patients who died had concomitant chronic hepatitis B infection and another 107 (28%) deaths occurred in patients with underlying HBsAg negative chronic liver disease, mostly nonalcoholic cirrhosis. Assuming a HBsAg carrier rate of 0.2% in the United States, Keefe (2) concluded that the case fatality rate of hepatitis A in HBsAg carriers was 58-fold higher than in the normal population. There should have been 231 HBV carriers among the 115,551 cases of acute hepatitis A resulting in a case fatality rate of 11.7% (27 deaths/231 patients) compared to 0.2% in HBsAg negative subjects (274 deaths in the remaining 115.320 patients). Two hypotheses might explain the differences between mortality rates of HAV superinfection on chronic hepatitis B in China and the United States.

a) In the US patients with hepatitis A are significantly older, i.e. the rate of nonimmune individuals in age groups over 14 years is higher resulting in a higher overall mortality of HAV.
b) HBV is usually acquired perinatally in China and during adulthood in the US, resulting in more inflammatory activity of chronic hepatitis in the US patients.

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Therefore it appears, that age at infection and the degree of inflammatory actitivity of chronic hepatitis B are important determinants of the clinical outcome of hepatitis A in chronic hepatitis B.

In 2 studies the clinical course of acute hepatitis A in patients with and without chronic hepatitis B was assessed on the basis of laboratory parameters. In a prospective study from Greece 14 out of 90 inpatients with acute hepatitis A were chronic HBsAg carriers, and another 9 had recovered from HBV infection (4). The remaining 67 patients served as controls. Peak ALT values in HBsAg carriers (1442 ± 650 U/l) and in anti-HBs positive patients (1369 ± 742 U/l) were significantly higher than in the control group (842 ± 464 U/l). There was no difference in the mean serum bilirubin levels, and no deaths were observed. These data assume that acute hepatitis A causes more severe liver cell damage in patients with chronic hepatitis B, but the finding of higher elevation of ALT levels in patients who have recovered from hepatitis B infection is difficult to explain. In another report from Japan 6 HBsAg positive patients with acute hepatitis A (3 chronic hepatitis B and 3 HBsAg carriers with normal liver function) were compared with a control group of 80 hepatitis A patients without HBV markers. Another 23 patients who had been reported in the Japanese literature were included in the analysis (5). Comparison of the 6 HBsAg positive patients with the control group revealed higher serum bilirubin levels (6.3 mg/dl vs 5.7 mg/dl), AST levels (2120 U/l vs 1342 U/l) and ALT levels (2148 U/l vs 1473 U/l) without reaching statistical significance. In 17 of the 29 patients with combined infection liver biopsy was available. Five had acute viral hepatitis, three had massive hepatic necrosis, five had chronic hepatitis and four had cirrhosis. In 16 patients analysed for this marker HBsAg titers decreased but returned to baseline after 2-4 weeks. Three patients lost HBsAg and 2 of them became anti-HBs positive. Two of the 29 patients analysed (7%) died of fulminant hepatic failure, one of them suffered from HDV superinfection. The patients regarded as healthy "HBsAg carriers" showed the same benign course of disease as patients without underlying liver disease.

Other studys were not able to confirm a more severe disease in patients with combined infection of hepatitis A and B (6,7,8,9,10).

During an outbreak of hepatitis A in 1982 in Taiwan all 143 affected patients were between 5 and 30 years old (6). 28 patients (20%) were HBsAg positive. There was no difference in the biochemical and clinical findings in HBsAg positive and negative patients. This fact may be explained by the young age of the affected patients which commonly results in a more favourable outcome in acute hepatits A, and the fact that younger patients are more likely to be healthy HBsAg carriers than to have chronic active hepatitis.

A study by Zachoval *et al.* (7) from Germany describes 30 chronic HBV-carriers with acute hepatitis A and 2 patients with simultaneous HAV and HBV infection. Risk factors identified were intravenous drug abuse in 9 patients and mediterranean origin in 17 patients. Mean peak ALT level (676 ± 547 U/l) and serum bilirubin (77 ± 43 umol/l) did not differ from the results in the large studies of hepatitis A alone in other countries, but there was no control group in the German study. This fact limits the author's conclusion that patients with underlying liver disease do not exhibit a more severe course of acute hepatitis A.

Tassopoulos *et al.* (8) reported a series of 356 acute hepatitis A infections in a Greek hospital between May 1981 and March 1984. Ten asymptomatic HBsAg carriers (2.8%) and four patients with acute hepatitis B (1.1%) were identified. These patients showed no difference in clinical outcome, as well as in biochemical and serological parameters than patients with hepatitis A alone. All 4 patients with hepatitis A and B cleared HBsAg and became anti-HBs positive.

In small case series and case reports, both more severe and similar clinical outcomes have been reported in patients with acute hepatitis A and chronic hepatitis B (9,10,11,12,13).

Patients with chronic hepatitis C

The risk of hepatitis A superinfection in chronic hepatitis C was recently investigated in a prospective study (14). Vento *et al.* followed 595 adults (163 with chronic hepatitis B and 432 with chronic hepatitis C) who were seronegative for anti-HAV IgM and IgG antibodies for 7 years. Twenty-seven patients acquired HAV superinfection (10 patients with chronic hepatitis B and 17 with chronic hepatitis C) during the study. One patient with chronic hepatitis B and liver cirrhosis developed severe cholestatic hepatitis, the other nine HBV carriers had an uncomplicated course of the disease. Two of these patients had the HLA phenotype A1, B8, DR3 and hypergammaglobulinemia. None of these patients seroconverted to anti-HBs or anti-HBe. Seven patients with chronic hepatitis C developed fulminant hepatic failure and 6 of them subsequently died. None of them had liver cirrhosis. Four of these patients had traveled to foreign countries within the suspected incubation period. In the other three patients no risk factor for HAV infection could be identified. Two had a history of former intravenous drug abuse, 3 had transfusion acquired hepatitis C and 2 HCV infections were community-acquired. Autopsy revealed massive liver-cell necrosis in the patients who died. Four of the patients with fulminant course of hepatitis A had the A1, B8, DR3 HLA phenotype compared with 9 of 191 control subjects (4.7%) with acute hepatitis A alone. None of these four patients had HGV infection. The other three patients with fulminant liver failure were HGV positive but had HLA phenotypes not suspective for autoimmune disease. The other 10 HCV patients had uncomplicated courses of hepatitis A. None of them had an autoimmune HLA phenotype and two

were positive for HGV-RNA before and during hepatitis A. Although HCV-RNA titers decreased during hepatitis A and became undetectable in 7 out of 10 patients, no patient lost HCV-RNA after recovery from hepatitis A. The authors concluded that hepatitis C virus does not contribute to fatal outcome since viral load decreased during HAV infection. It was suggested, that a high incidence of autoantibodies in patients with fatal outcome might reflect autoimmune mechanisms which in susceptible patients are partly primed by HCV-infection and triggered by HAV-superinfection as recognized by the HLA phenotype A1, B8, DR3. The other 3 patients with fulminant hepatic failure did not exhibit autoimmune features, but all were coinfected with HGV. The authors concluded that patients with chronic hepatitis C have a substantial risk for fulminant hepatic failure in case of hepatitis A superinfection and that vaccination against hepatitis A should be recommended.

Patients with nonviral chronic liver disease

CDC data of clinical outcome of acute hepatitis A suggest that underlying nonviral liver disease may worsen the course of HAV infection. 107 (28%) out of 381 deaths in 115,551 HAV cases were associated with chronic primarily nonalcoholic liver disease. Akriviadis *et al.* reported 4 cases of fulminant liver failure with subsequent death due to acute hepatitis A in patients with drug abuse and alcoholic liver disease (15).

Hepatitis A vaccination in chronic liver disease

Hepatitis A vaccination using inactivated vaccines was established in the early ninetees (16,17). Recently, a study was performed to establish the safety and immunogenicity of a hepatitis A vaccine (HAVRIX®) in patients with different types of chronic liver disease. The results were presented at the 32nd Annual Meeting of the EASL 1997 in London. Patients received 2 injections of 1440 IU at month 0 and 6. At month 1 93,5% of subjects in the healthy control group had seroconverted compared with 75% in the HCV group. At month 6, prior to the second injection, 72.6% were seropositive in the healthy control group compared with 39.1% in the HCV group. At month 7, one month after the second injection, the seropositivity rates were almost identical (98.1% vs 95.1%). Vaccination was well tolerated in all treatment groups.

Conclusion

The question whether or not acute hepaitis A causes a more severe clinical course in patients with underlying liver disease or increases the risk of fatal liver failure cannot be answered definitely. Data from an epidemic outbreak of hepatitis A and surveillance data from the United States as well as the conclusions from smaller case series and case reports suggest that patients with chronic hepatitis B as well as patients with nonalcoholic cirrhosis may exhibit a more severe disease, a higher risk of fulminant liver failure and a higher case fatality rate, especially when histological abnormalities exist. The increased mortality rate during the Chinese epidemic and in the United States (approximately 6 and 58 fold) suggests that older age and inflammatory activity of underlying chronic hepatitis B may be the major factors determining outcome. The high risk of fulminant hepatic failure in patients with chronic hepatitis C, as reported from Italy, should be confirmed by larger and prolonged studies. Nevertheless, these data strongly support a role of hepatitis A superinfection in the induction of fulminant liver failure in patients with chronic hepatitis C. Hepatitis A vaccination is safe and effective and should be advocated on patients with chronic liver disease. Studies are needed to investigate the long-term protection potential of the vaccine in patients with chronic viral hepatitis.

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