Relapse of acute B viral hepatitis – role of delta agent

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SUMMARY Serologic markers for delta agent were evaluated in 39 patients with acute hepatitis B and clinical relapse within 30 days from the initial episode. Eighteen of the 39 patients (46%) had evidence of acute delta infection. Delta antigenaemia preceded the appearance of antibodies in seven of these 18 patients; delta antigenaemia occurred during the initial episode of illness and the appearance of the antibody coincided with the relapse. Eight of these patients developed severe relapse with fulminant course which resulted in two deaths. This study reveals that delta infection is one of the important causes of severe relapse in cases of acute B viral hepatitis.

Infectivity studies in chimpanzees have shown that simultaneous infection with delta agent and hepatitis B virus (HBV) can result in a peculiar sequential expression associated with bimodal disease.¹ Multiple episodes of serum aminotransferase (ALT) rises have been reported as a feature of acute hepatitis among drug addicts using parenteral route.^{2,3} The prevalence rate of delta infection has been reported to be high in the same group.⁴⁻⁷ Hence, the two bouts of ALT rises occurring a few weeks apart in these patients probably represents a biphasic hepatitis from co-infections of HBV and delta agent. In order to investigate this possibility and to establish the sequential serologic events in patients with concurrent HBV and delta infection, sera from 39 patients with biphasic acute hepatitis were examined for all the markers of delta. A significant number of these patients with biphasic or relapse of acute hepatitis showed evidence of acute delta infection.

Methods

PATIENTS

Serial serum samples were available from the onset of initial illness in 39 patients with a clinical diagnosis of relapse of acute B hepatitis. The relapse occurred within four weeks of the initial illness in all these patients. The majority of these patients (80%) were found to be intravenous drug addicts.

CONTROL GROUP

Sera from 45 consecutive intravenous drug users with acute B hepatitis, whose clinical course was not associated with relapse were also studied for delta and HBV markers.

SEROLOGICAL TESTS

HBsAg was detected by radioimmunoassay (Ausria II, Abbott, North Chicago, Illinois, USA). Anti-HBc IgM was detected by a solid phase RIA (SPRIA) IgM capture assay at 1/1000 dilution.⁸ Delta antigen was detected by SPRIA in serum samples treated with Nonidet P40 as described previously.⁹ Anti-delta IgM and IgG was quantified as described previously.¹⁰

STATISTICAL ANALYSIS

The comparison of the prevalence of delta markers among those with relapsing B hepatitis and those without relapse, was analysed by χ^2 test with Yates' correction. The results of liver function tests during the initial illness and at time of relapse were compared using the Student's *t* test for paired values.

Results

All 39 patients in the study had circulating HBsAg and anti-HBc IgM, hence representing acute B viral hepatitis. Eighteen of the 39 patients showed serologic evidence of acute delta infection as follows: seven of 18 patients had initial delta antigenaemia coinciding with the first peak of ALT activity followed by the appearance of antidelta coinciding with the second ALT peak, the relapse

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Fig. 1 Serologic markers for delta in relation to the ALT peaks and prothrombin time in one representative patient.

(Fig. 1). Antigenaemia lasted between two to seven days in these patients and the antibody appeared by 11–18 days after the disappearance of the antigen. Another seven of the 18 patients had no detectable period of antigenaemia but nonetheless antidelta appeared coincident with the second peak of ALT rise. In the remaining four (four of 18) patients, antidelta was identifiable during the time of the first peak of ALT activity.

The order of appearance of antidelta IgM and IgG was as follows: antidelta IgM first followed by antidelta IgG in four of 18; appearance of antidelta IgM class alone without the IgG class appearance in two of 18; both IgM and IgG classes of antidelta appearing at the same time of testing in 12/18. Of the 45 patients (control group) with acute B hepatitis without relapse only five patients had serologic evidence of acute delta infection. Hence the prevalence of delta infection among those with relapse was significantly higher than those without relapse ($p < 0.01$).

CLINICAL COURSE AND FOLLOW UP

Majority of the patients with evidence of acute B and delta infections had significantly prolonged prothrombin time ($p < 0.001$) during the relapse than during the first episode (Fig. 2). Although the serum ALT concentrations were higher during the relapse, they were not significantly different ($p < 0.01$) from those of the first episode (Fig. 3). Of these 18 patients four developed fulminant hepatitis and two died.

Follow up serum samples were available at 20

Fig. 2 Prothrombin time expressed as percentage of normal in seven of the 18 patients with concomitant B and delta hepatitis.

days to 105 days from the onset of illness. There was clearance of serum HBsAg with the disappearance of antidelta in two of 18 patients at two months and four months respectively. In two other patients, there was rapid clearance of serum HBsAg on 13 and 18 days from the initial illness (Fig. 4). In these patients, this clearance coincided with the relapse

Fig. 3 Serum ALT concentrations in 12 of the 18 patients with concomitant B and delta hepatitis.

Fig. 4 Rapid clearance of HBsAg in one of the patients with concomitant B and delta hepatitis.

and the appearance of antidelta. They remained HBsAg negative during the follow up. In the remaining 14/18 patients the follow up was inadequate to document the clearance of HBsAg or the disappearance of antidelta. Two of these 14 patients died while their serum HBsAg and antidelta were still positive.

Discussion

Although relapse of acute viral hepatitis has been reported to occur in 1.8 to 15%,¹¹ thus far, there are no data available to reveal the causative factor involved.

From this study of 39 patients with relapse of acute type B hepatitis, it is evident that concomitant delta infection plays an important role in producing relapse. Of the patients with similar epidemiologic background, the prevalence of acute delta is significantly higher among those with clinical relapse than those without relapse ($p < 0.01$). It appears that the relapse of hepatitis caused by delta agent can result in severe degree of hepatic necrosis leading to hepatic failure. By examining the initial serum samples of patients with acute B hepatitis for the presence of delta antigen, one can probably speculate the occurrence of clinical relapse in association with the appearance of antidelta.

Purcell *et al*¹ in their infectivity studies of chimpanzees hypothesised that in cases of coinfections of HBV and delta with biphasic illnesses, the first enzyme peak was probably caused by HBV induced hepatic necrosis and the second by delta induced necrosis. In their study, there was a close correlation between the appearance of delta antigen in serum and the onset of hepatitis. Among the patients reported currently, transient delta antigenaemia coincided with the first peak. If the first enzyme peak is because of liver necrosis in association with

delta antigenaemia, it is difficult to explain the basis of liver necrosis causing the second peak. It might be related to immune mediated necrosis because of hepatitis B virus. The appearance of antidelta coinciding with the second enzyme peak in 14/18 patients, is highly suggestive of a possible role of this antibody in the hepatic necrosis and enzyme rise. This is contrary to the currently available data, however, based on the morphologic changes that delta is a cytopathic virus and that there is no immune mediated reaction.¹²

Rapid clearance of serum HBsAg in two of our patients by days 13 and 18 of the illness, in association with the appearance of antidelta and second ALT peak, is suggestive of an extreme degree of suppression of HBV activity because of the associated delta hepatitis. Previous reports have shown such inhibitory effect of delta agent on HBV replication in patients with chronic B infection.^{13 14} Acute delta superinfection resulted in the clearance of serum HBsAg in three of our chronic HBV carriers (personal communication).

Unfortunately, owing to the lack of follow up studies in most of the cases reported here, we cannot evaluate the natural course of concomitant acute B and delta hepatitis. According to the previous reports, the majority of patients with concomitant B and delta infections, have self limiting illnesses, and do not develop chronic forms of hepatitis.^{15 16}

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