In erythrocytes treated with lithium the choline transport system is inhibited bidirectionally, and hence choline derived from phosphatidylcholine catabolism within the cell would increase. Phospholipase D activity in human erythrocytes has been indicated from nuclear magnetic resonance studies,[14] and the activity of this enzyme would be responsible for the raised choline concentrations.

The raised cholesterol concentrations are consistent with other reports of hyperlipoproteinaemia[15] in cluster headache and may be contributory to the higher incidence of coronary heart disease seen in these patients.[16] Abnormal thyroid function was unlikely to be the cause of the raised cholesterol concentrations since there was no noticeable increase in T4 or thyroid stimulating hormone in non-lithium treated patients. The raised circulating thyroid stimulating hormone concentrations found in some patients receiving lithium is in keeping with the benign thyroid enlargement that occurs occasionally during this treatment.

Although our work has yielded significant results which may provide a marker in cluster headache and also give some insight into the cause of the disorder, several important questions remain. Firstly, it would be of great interest to determine whether abnormal concentrations of choline are found in migraine, which is clearly distinguishable from cluster headache by the attack profile and response to treatment. Lithium is not helpful in migraine and may even exacerbate the condition,[17] so that it would be useful to study whether differences in patients with migraine are reflected in erythrocyte choline values. Secondly, it would be important to examine erythrocyte concentrations of choline in patients with chronic cluster headache and the small proportion of patients with cluster headache who do not respond to lithium to determine whether the correlation extends to these conditions.

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Multiplication of hepatitis B virus in fulminant hepatitis B

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Abstract

The presence in serum of hepatitis B e antigen (HBeAg) and hepatitis B virus DNA, which are each regarded as reflecting multiplication of hepatitis B virus, were looked for one to five days after the onset of hepatic encephalopathy in 64 patients with fulminant hepatitis B. HBeAg and hepatitis B virus DNA were found in the serum of only 24 (37%) and six (9%) patients, respectively. Hepatitis B virus DNA was absent from the serum in all 13 patients positive for anti-HBs.

These findings indicate that replication of hepatitis B virus stopped after the onset of hepatic encephalopathy in most of the patients and support the view that an enhanced immune response stops the replication. Agents that inhibit viral multiplication would probably not have any effect at this stage of the disease.

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Introduction

Fulminant hepatitis B is an uncommon but severe complication of acute infection with hepatitis B virus. Mortality among adults with fulminant hepatitis B is 82%[1] and has not been appreciably reduced by any of the numerous drugs and procedures that have been proposed for treatment of the disease.[2 3] Agents

inhibiting viral multiplication have been envisaged for such treatment, but the use of such agents is justified only if multiplication of hepatitis B virus is still occurring. Fast clearance of hepatitis B surface antigen (HBsAg) from serum has been reported in fulminant hepatitis B and attributed to an enhanced immune response,[4 5] but it may be associated with the cessation of multiplication of hepatitis B virus or, alternatively, persistence of such multiplication and synthesis of HBsAg masked by massive production of anti-HBs. To determine whether multiplication of hepatitis B virus stopped or persisted we looked for the presence of hepatitis B e antigen (HBeAg) and hepatitis B virus DNA in the serum of patients with fulminant hepatitis B. The presence of either of these markers in serum is regarded as reflecting multiplication of hepatitis B virus.[6-10]

Patients and methods

We investigated 64 patients (26 men, 38 women) with fulminant hepatitis B who were admitted to Hôpital Beaujon from 1972 to 1981. The mean age was 39 (range 15-80). Fifty one of the patients died. Fulminant hepatitis B was diagnosed if the following criteria were satisfied: (*a*) the patient had jaundice; (*b*) hepatic encephalopathy developed less than two months after the onset of jaundice; (*c*) serum aminotransferase activity was more than 10 times the upper limit of the normal range; (*d*) no drugs known to be deleterious to the liver had been injected or ingested; (*e*) IgM antibody to hepatitis A virus was absent (hepatitis A virus AB-M, Abbott); (*f*) HBsAg (Ausria II, Abbott) and IgM anti-HBc (Corzyme-M, Abbott) were present in serum; and (*g*) histological examination of a specimen of hepatic tissue taken by transjugular liver biopsy[11] or at necropsy showed extended hepatocyte necrosis and no lesion of chronic liver disease.

Serum samples were collected one to 58 days after the onset of jaundice—that is, one to five days after the onset of encephalopathy. On the day of collection all the patients had clinical manifestations of hepatic encephalopathy. The serum samples were stored at −20°C and were later tested for HBeAg by radioimmunoassay (HBe, Abbott), for hepatitis B virus DNA by molecular hybridisation,[10] and for anti-HBs by radioimmunoassay (Ausab, Abbott).

Results

HBeAg and hepatitis B virus DNA were found in serum from 24 and six, respectively, of our 64 patients with fulminant hepatitis B (table). Of the 40 patients whose serum samples were collected less than 10 days after the onset of jaundice, six were positive for hepatitis B virus DNA, of whom five were also positive for HBeAg; of the 24 patients whose serum samples were collected more than 10 days after the onset of jaundice, none were positive for hepatitis B virus DNA. Anti-HBs was found in 13 patients, all of whom were negative for hepatitis B virus DNA. None of the six patients positive for hepatitis B virus DNA survived, while 13 of the 58 patients negative for hepatitis B virus survived; this difference was not significant.

Presence or absence of HBeAg and hepatitis B virus DNA in serum from 64 patients with fulminant hepatitis B

No of patients	HBeAg	Hepatitis B virus
39	−	−
19	+	−
5	+	+
1	−	+

Discussion

Our finding of HBeAg and hepatitis B virus DNA in the serum of only 37% and 9%, respectively, of our patients with fulminant hepatitis B indicates that multiplication of hepatitis B virus, which probably took place at an early stage of acute infection with hepatitis B virus, had stopped after the onset of hepatic encephalopathy in most of them. This view is reinforced by our findings of hepatitis B virus DNA in 12·5% of the serum samples collected before, but in none of those collected after, the 10th day of jaundice.

The fact that a higher proportion of patients were positive for HBeAg than for hepatitis B virus DNA might indicate that, after multiplication of hepatitis B virus has stopped, hepatitis B virus DNA disappears from serum faster than HBeAg. Such an interpretation has been proposed previously to account for the higher proportion of patients positive for HBeAg than of patients positive for hepatitis B virus DNA[10] (or DNA polymerase[12]) among patients with chronic hepatitis positive for HBsAg.

Anti-HBs was found in 20% of our patients, a proportion similar to that found in one series of patients with fulminant hepatitis B[4] but lower than that reported in another.[5] Hepatitis B virus DNA was absent from the serum in all of our patients in whom anti-HBs was present, which suggests that multiplication of hepatitis B virus may stop owing to the enhanced immune response.

The fact that multiplication of hepatitis B virus stopped in most of the patients with fulminant hepatitis B suggests that agents inhibiting viral multiplication would have little effect at this stage of the disease. The fairly high number of survivors in a small series of patients with fulminant hepatitis B given leucocyte interferon[13]—if not a fortuitous coincidence—might be attributable to an effect unrelated to inhibition of viral multiplication.[14]

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