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Interferon therapy for chronic non-A non-B and chronic delta liver disease in haemophilia

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Summary. The case histories of a carrier of haemophilia A with chronic post transfusion non-A non-B hepatitis and a severe haemophiliac with chronic delta hepatitis are described. Therapy with lymphoblastoid alpha interferon resulted in improvement of NANB and HDV related chronic hepatitis and resolution of HIV related thrombocytopenia. Interferon may modulate replication of more than one transfusion transmitted virus in the haemophiliac.

Transmission of hepatitis B virus (HBV), hepatitis delta virus (HDV) and non-A non-B (NANB) viruses by transfusion of unheated clotting factor concentrates are well documented. All of these viruses can cause chronic liver disease and cirrhosis.

Prospective studies of post-transfusion hepatitis have shown that 50% of patients with acute NANB hepatitis develop chronic liver disease (Alter & Hoofnagle, 1984). Furthermore, 10–25% of patients with chronic NANB hepatitis have developed cirrhosis (Alter & Hoofnagle, 1984; Realdi *et al*, 1982). Whilst some investigators have found corticosteroids to be beneficial (Realdi *et al*, 1982), others have found this treatment ineffective (Rakela & Redeker, 1979; Hoofnagle, 1981; Alter & Hoofnagle, 1984). More recently antiviral agents have been used. A preliminary report of the treatment of chronic NANB hepatitis with recombinant human alpha interferon was reported in 1986 (Hoofnagle *et al*, 1986).

Superinfection of chronic HBV carriers with HDV often progresses to chronic HDV infection with accelerated liver damage and development of cirrhosis. A study by Rizzetto (1983) has shown that 60–70% of cases lead to cirrhosis and that the annual mortality from this chronic infection is 1–3%. The use of alpha-Interferon in the therapy of HDV has been reported (Hoofnagle *et al*, 1985; Thomas *et al*, 1986; Rosina *et al*, 1986) and it is probable that alpha-interferon inhibits HDV replication.

The therapy with lymphoblastoid interferon (Wellferon) for chronic NANB hepatitis in a carrier of haemophilia A and of HDV hepatitis in a patient with severe haemophilia A are reported here.

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RESULTS

Patient 1 (Figs 1 and 2)

The clinical history and course of this patient have been reported previously (Lee *et al*, 1985). A known carrier of haemophilia A, with a basal level of 16 U/dl factor VIII:C, she developed acute fulminant NANB hepatitis 8 weeks after transfusion with cryoprecipitate as treatment for evacuation of a haematoma in the right prepatellar region (Fig 1). For 2 years following the acute illness the patients was seen regularly as an outpatient and complained of malaise, tiredness and epigastric discomfort. A liver biopsy was performed 2 years after the episode of acute hepatitis under cover of deamino 8D arginine vasopressin (DDAVP) and cryoprecipitate and this showed mild chronic active hepatitis.

At the beginning of 1984 (3 years after the acute fulminant hepatitis) the patient was symptomatic with abnormal levels of asparate transaminase (AST) (Fig 2). This continued until August 1987 when lymphoblastoid interferon was started at a dose of 5 million units (mU) three times weekly subcutaneously. There was a rapid reduction in the level of AST activity (Fig 2). The dose of interferon was gradually reduced to 1·5 mU three times weekly. On one occasion in February 1988, the patient inadvertently reduced her dosage to 0·75 mU for four injections. There was a prompt rise in the AST activity. Subsequently, when a further dose reduction to 0·5 mU three times weekly was attempted there was also a rise of AST level. When the interferon was stopped for a trial period there was a prompt rise of the AST activity to 316 u/l. In this patient the dose

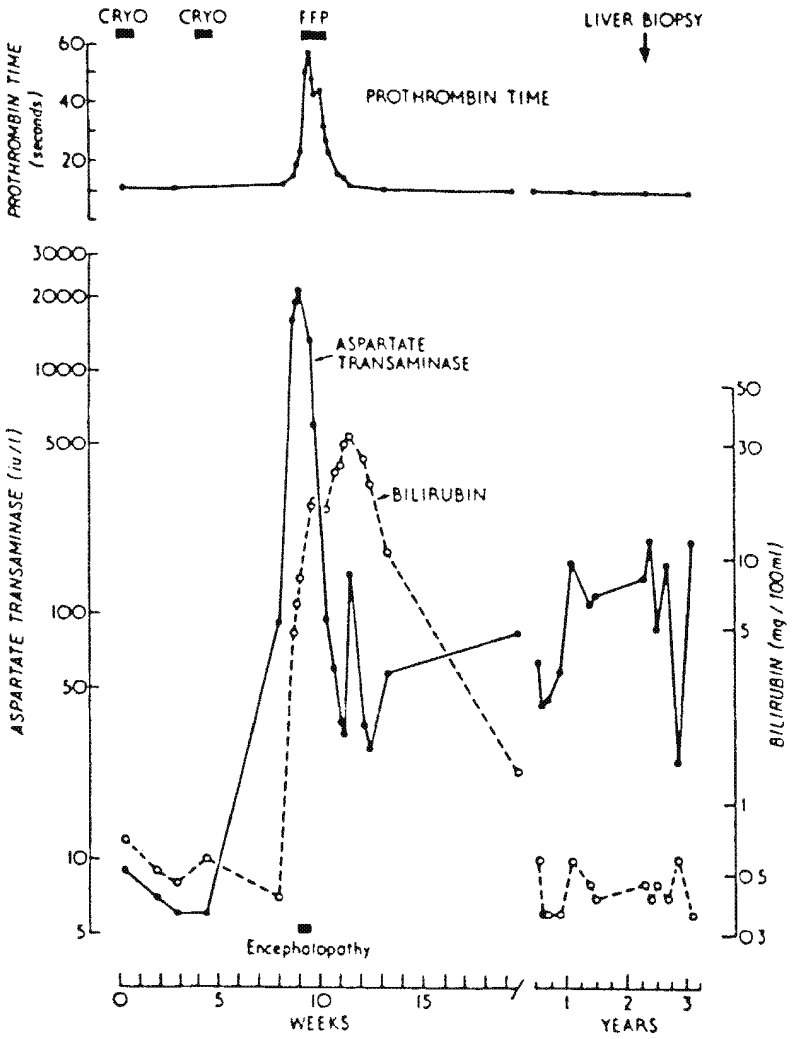

Fig 1. Changes in liver function tests and their relationship to treatment and clinical events in a carrier of haemophilia who developed fulminant NANB hepatitis after treatment with cryoprecipitate.

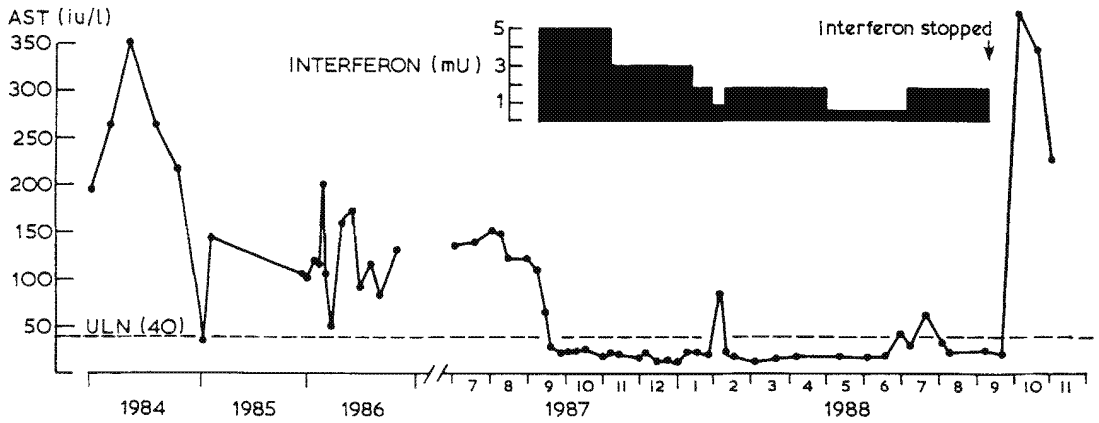

Fig 2. Interferon treatment for chronic post-transfusion non-A non-B hepatitis. ULN = upper limit of normal.

required to maintain a normal AST level is 1·5 mU three times weekly.

Before treatment the patient was symptomatic from her chronic hepatitis. Since treatment, she has experienced general well-being.

Patient 2 (Figs 3 and 4)

The clinical history of the patient has been previously reported (Lee *et al*, 1985). The patient has severe haemophilia A and in 1976, when he was 14 years old, he was first exposed to commercial factor VIII concentrate and developed

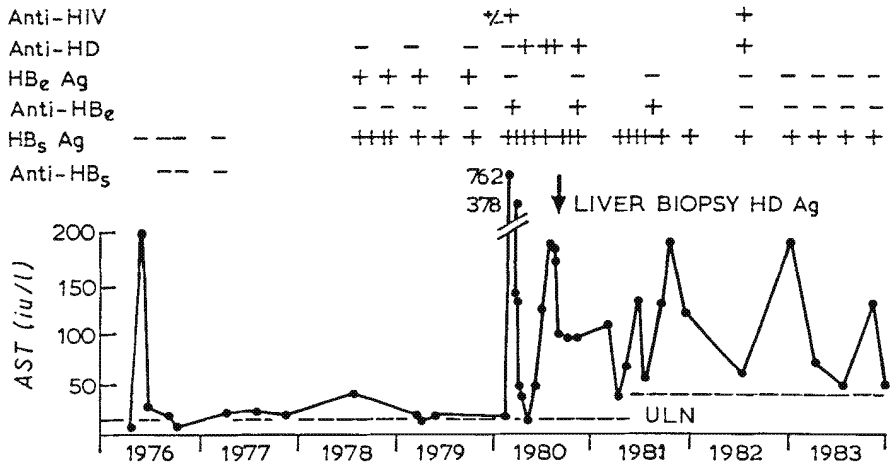

Fig 3. The relationship between HBV and delta agent in a patient with haemophilia A. ULN = upper limit of normal.

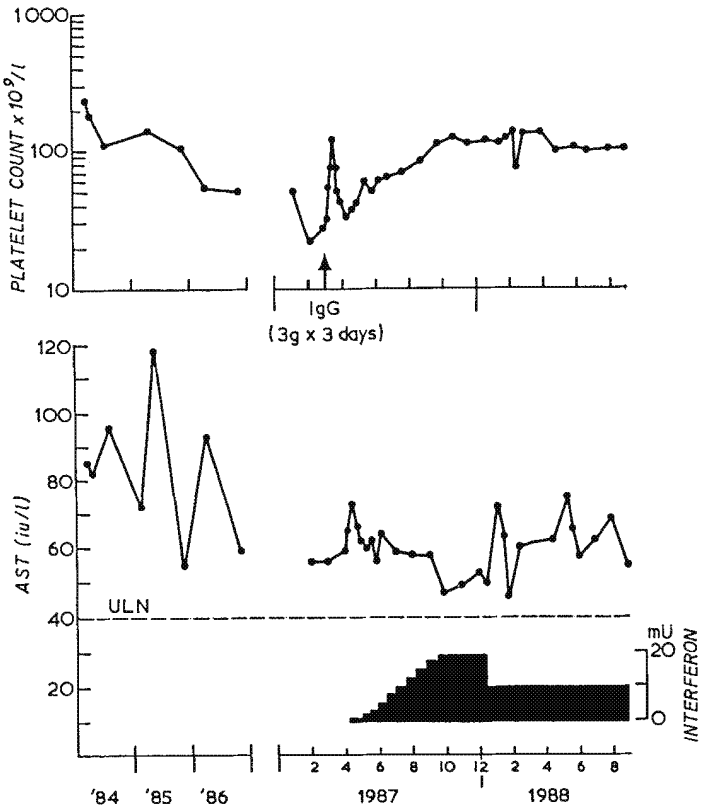

Fig 4. Interferon treatment in a patient with haemophilia infected with several viruses.

NANB hepatitis (Fig 3). He was found to be HBsAg and HBeAg positive at the age of 15 years when his mother developed acute hepatitis B as a result of a needlestick injury. In 1980, aged 18 years, he developed acute hepatitis. At this time he acquired both HDV and HIV infection and had seroconverted from HBeAg to anti-HBe sometime during the preceding 5 months. A liver biopsy showed features of lobular hepatitis and was positive for HDVAg.

The patient remained clinically well and there was no hepatosplenomegaly on CT scan. In 1987, the patient was HBsAg positive, but HBeAg and HBV-DNA negative. Although HDAg had been demonstrated previously in the liver biopsy (1980), and the patient was anti-HD positive, no HDV-RNA could be detected in the serum.

At the beginning of March 1987, the patient had a platelet count of 22×10^9/l (Fig 4). This persisted and a bone marrow performed at the beginning of April was hypercellular consistent with peripheral destruction of platelets. This was thought to be HIV-related. Treatment with immunoglobulin (30 g daily for 3 d) was given. Although there was an initial response (Fig 4), the platelet count rapidly fell and was 34×10^9/l at the beginning of May.

At this time there were anecdotal reports that interferon helped HIV-related thrombocytopenia (Ellis *et al*, 1987; Lever *et al*, 1987), and this prompted treatment with interferon which it was hoped would also modulate the HDV and NANB chronic hepatitis.

Treatment with lymphoblastoid interferon was started at the beginning of May 1987 in a dose of 1 million units (mU) three times a week which the patient administered intravenously. The dose was gradually increased to 19 mU three times weekly by week 25 (Fig 4). Initially the patient experienced back pain and pyrexia following treatment, but he continued well until the dose reached 17·5 and 19 mU three times weekly, when he again experienced malaise, tiredness, aching and rigors. After 9 months of treatment the does was maintained at 10 mU three times weekly without severe side-effects. A record of the AST activity (iu/l) is shown in Fig 4 and this shows improvement of the level although the values did not reach the normal image. The platelet count gradually rose and reached a plateau of approximately 100×10^9/l after 5 months of treatment.

DISCUSSION

Previous studies indicate that Wellferon inhibits both NANB and HDV replication (Lever *et al*, 1987; Thomas *et al*, 1986). The rapid improvement in the level of the aspartate transaminase shown in both out patients who had NANB hepatitis supports the concept that the hepatocellular injury in chronic NANB hepatitis is a direct result of virus replication (Hoofnagle *et al*, 1986). The small peaks of AST activity which occurred on reduction of the dose and the large rise in AST which occurred after stopping interferon in patient 1 suggest that the treatment will need to be continued long-term. This is acceptable treatment for this patient who has no side-effects at the low dose of 1·5 mU three times a week.

The largest study of the treatment of chronic delta hepatitis with interferon has come from Italy where HDV is common (Rosina *et al*, 1986). In this study during treatment with interferon the serum aminotransferase levels improved in 58% of patients and HDV RNA disappeared in 67%. However, the improvement of chronic hepatitis as demonstrated by transaminase levels is not maintained after stopping therapy with interferon in chronic HDV (Hoofnagle & DiBisceglie, 1988). It is probable that interferon has an inhibitory effect on HDV replication and that interferon therapy will be required long-term or possibly permanently.

Patient 2 has been shown to be infected with at least four transfusion transmitted viruses: NANB, HBV, HDV and HIV. Interferon therapy not only resulted in an improvement of the transaminase level which presumably represented an effect on NANB and HDV replication, but there was also a resolution of the HIV-related thrombocytopenia. There have been other reports of the successful use of interferon in AIDS-associated thrombocytopenia (Ellis *et al*, 1987; Lever *et al*, 1987), and also in severe unresponsive immune thrombocytopenic purpura (Proctor *et al*, 1988). Splenectomy in the face of thrombocytopenia is hazardous for the patient with haemophilia. Treatment with steroids may increase the risk of infection for the patient with HIV infection. Thus, interferon is a suitable therapy for thrombocytopenia in this situation.

Interferon could thus represent a useful therapy in the multi-transfused haemophiliac who can conveniently self-administer the treatment intravenously. In such patients it may stop the replication of more than one virus and control some of the associated phenomena of HIV infection.

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