Recurrent Acute Hepatitis Following the Use of Factor VIII Concentrates

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During a 3-yr period, a patient with hemophilia A experienced 5 episodes of acute hepatitis within 7–16 days following 5 separate infusions of factor VIII (FVIII) concentrates. Although the exact mechanism of the recurrent hepatitis remains unclear, these episodes most likely represented repeated allergic reactions to an antigenic protein derived from the FVIII concentrates. Although no evidence was found for a specific humoral immune response to FVIII in the circulation of this patient, an isolated cellular immune response was suggested by the finding of in vitro lymphocyte stimulation in response to the FVIII concentrate. This unusual type of posttransfusion hepatitis must be added to the list of adverse responses to FVIII concentrates.

Factor VIII (FVIII) concentrates have been available for the treatment of hemophilia for over a decade. Adverse reactions associated with their use include chills, fever, hypersensitivity reactions characterized by urticaria and angioedema, bronchospasm, anaphylaxis, nausea, headache, visual disturbances, and possibly splenomegaly.1–3 However, the most frequent complication of FVIII concentrate therapy is live disease, including acute and chronic hepatitis4–14 and isolated abnormalities of liver function tests.3–7 The cases of hepatitis associated with the use of FVIII concentrates have been related to hepatitis B virus (HBV)4–13 and, most commonly, hepatitis non-A, non-B virus (H non-A, non-BV).4–10,14 In addition, patients with serologic evidence of prior HBV infection in the absence of previous overt hepatitis have been described frequently.4–6,11,12

Recent reports have described patients with multiple attacks of acute viral hepatitis, including three patients with four separate episodes.14,15 In one series, at least one episode in each of 12 patients was accompanied by serologic documentation of HBV infection.15 In another study of six children with hemophilia, recurrent episodes of “short-incubation” hepatitis (incubation periods of 4–19 days) were attributed to H non-A, non-BV.14

The opportunity to study a patient who experienced 5 episodes of short-incubation (7–16 days), seronegative acute hepatitis has allowed us to present an alternative hypothesis for the mechanism of liver injury in some hemophilic patients with recurrent hepatitis. We believe that the episodes of hepatitis in our patient may have represented allergic hepatitis due to a protein contaminant of the FVIII concentrate, and we wish to alert physicians to this potential complication of FVIII concentrate therapy.

CASE REPORT

A 25-yr-old teacher was diagnosed in 1956 as having mild hemophilia A (factor VIII coagulant activity 14 U/100 ml, normal 62–224; factor VIII antigen 168 U/100 ml, normal 60–185). Between 1956 and 1973 he received no specific treatment for infrequent and mild bleeding episodes. On June 18, 1973, at age 42, after sustaining a major hemarthrosis, he received his first infusion of FVIII concentrate, Profilite (Antihemophilic Factor [Human], Abbott Scientific Products Division, Abbott Laboratories, North Chicago, Ill.). Sixteen days later he developed chills, mild fever, lethargy, nausea, pale stools, and dark urine. Physical examination revealed scleral icterus and hepatomegaly but no splenomegaly. Liver function studies showed the following: serum glutamic oxalacetic transaminase (SGOT), 410 IU/liter (normal <20); serum glutamic pyruvate transaminase (SGPT), 710 IU/liter (normal <15); total bilirubin, 6.3 mg/dl (normal <1.5); direct bilirubin, 4.2 mg/dl (normal <0.6); and alkaline phosphatase 210 IU/liter (normal 20–90). Tests for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and heterophile antibody were negative. He was much improved symptomatically 4 wk after the concentrate infusion but remained icteric until November of 1973. The essential data from this episode of hepatitis and 4 subsequent episodes occurring after infusions of FVIII are illustrated in Fig. 1. The lag time between the concentrate infusion and the onset of hepatitis shortened progressively with the first 4 episodes from 16 to 7 days (16, 15, 9, and 7 respectively). The fifth episode was precipitated by spontaneous bleeding into the patient’s right thigh on January 31, 1976 (Fig. 1.). In an attempt to prevent a recurrence of hepatitis, the patient was treated with a different FVIII concentrate, Hemofil (Antihemophilic Factor [Human], Hyland Division, Travenol Laboratories, Inc., Costa Mesa, Calif.) and was simultaneously begun on prednisone therapy (40 mg/dl initially, decreased and discontinued over 7 days). Twenty days later, the SGOT was normal but the SGPT, LDH, direct bilirubin, and alkaline phosphatase were all mildly elevated. Although icterus occurred, the episode was comparatively mild and the patient remained relatively asymptomatic. Posttransfusion plasma samples revealed no evidence for a specific inhibitor to FVIII. A serum sample obtained after the last episode revealed quantitatively normal immunoglobulins, a low normal C3 level (124 mg/dl; normal 123–167) and a negative radioimmunoassay for HBsAg.

Although the patient’s lymphocytes were studied on several
occasions, only one experiment revealed a significant increase in DNA synthesis in response to high concentrations of FVIII concentrate (Fig. 2). The 30-fold increase in DNA synthesis of this patient's lymphocytes in response to Profilate was observed shortly after the fourth clinical episode. A consistent pattern of response was not observed thereafter. However, no stimulation could be demonstrated at any time among a population of 8 other patients with hemophilia tested with the same concentrate (Fig. 2). Counterimmunoelectrophoresis of the patient's serum against threefold dilutions of Profilate failed to reveal any stainable band of immune complexes, and a Clq-binding assay performed at a later date was within the normal range.

**DISCUSSION**

The most frequent complication associated with the use of FVIII concentrates is liver disease, most commonly due to repeated exposure to viral antigens in the concentrates. Clinically overt acute hepatitis due to the HBV has been documented in 4%–25% of multiple transfused hemophiliacs. Despite this low frequency of clinically acute hepatitis, serologic evidence of prior HBV infection (positive HBsAg, anti-HBs, or anti-HBc) has been demonstrated in 65% to more than 90% of hemophiliacs. Presently, H non-A, non-BV is probably the most frequent cause of posttransfusion acute hepatitis in association with the administration of FVIII concentrates, as with all other blood products. In addition, abnormal liver function tests have been demonstrated in 50%–70% of hemophiliacs receiving multiple infusions of FVIII concentrate. Moreover, chronic persistent and chronic active hepatitis (with or without cirrhosis) were discovered in 2%–16% of a population of hemophiliac patients with persistent liver enzyme elevations and positive HBsAg or anti-HBs. Also, hepatitis non-A non-BV has been implicated in the genesis of both chronic liver disease and recurrent hepatitis in hemophilia. In the most recent series of patients with recurrent hepatitis, the authors attributed the attacks to one or more H non-A, non-BV. Moreover, they suggested that evidence was lacking to support a hypersensitivity phenomenon as the cause of the hepatitis.

In light of the unique findings in the present case (5 separate episodes of documented short-incubation, seronegative hepatitis), however, we propose that an allergic mechanism may be implicated. It is extremely unlikely that the episodes in our patient were produced by a known virus. Neither HAV nor HBV infection is characterized by the short incubation period that was observed in this case (7 and 9 days for the third and fourth episodes, respectively). In addition, immunity to subsequent attacks of acute hepatitis with HAV and HBV apparently develop after the first infection. Although the incubation period of the first two episodes in our patient were consistent with an infection due to HAV, previous studies have shown that HAV is implicated only rarely in transfusion-associated hepatitis. Moreover, the absence of either the HBsAg or anti-HBs throughout our patient's course is further evidence against an infection caused by HBV. H non-A, non-BV infections might have caused episodes 1 and 2 in our patient, since incubation periods as short as 2 wk have been reported with this virus. However, the more usual incubation period for this virus is 6–9 wk, and one would have to implicate 5 different H non-A, non-B viruses to explain our patient's recurrent attacks. Although occasional cases of non-A, non-B hepatitis with...
episodic exacerbations have been described\(^{17,22}\) the return of liver function tests to normal and the complete resolution of symptoms within 1 mo of each episode in our patient would be highly atypical for this form of chronic liver disease. In addition, each episode in our patient was clearly related to the infusion of a FVIII concentrate. Neither EBV nor CMV can be implicated in our patient’s episodes of hepatitis, since tests for the heterophile antibody were negative and neither virus has been associated with recurrent attacks of posttransfusion hepatitis.\(^{18,22}\)

Although an undetermined, recurrent hepatotoxic exposure was considered, the typical features of a 1–2-day incubation period and an abrupt rise and rapid fall of the transaminases were absent.\(^{23}\)

In view of these arguments and the supportive evidence found in our patient, FVIII-concentrate-associated allergic or hypersensitivity hepatitis was entertained, although we recognized that this diagnosis was one of exclusion. We hypothesized that a foreign antigenic protein or stabilizing chemical contained in the FVIII concentrates could have bound to the patient’s hepatocytes or a structural protein of his hepatocytes and thus formed an immunogenic protein–hepatocyte complex. In view of the development of clinical hepatitis following the initial transfusion of concentrate, the patient must have been exposed to the putative antigen previously in some other form. Evidence for the antigenicity of FVIII concentrates has included the demonstration that lymphocytes from transfused hemophiliacs undergo DNA synthesis when exposed in vitro to FVIII concentrates,\(^{24}\) although we could not confirm this observation in a small group of patients with hemophilia (Fig. 2—hemophilic controls). We demonstrated a similar response, however, on one occasion in our index patient. Additional clinical evidence to support the allergic hypothesis in this case include: (1) the progressively shorter incubation period with each recurrent attack;\(^{20-25}\) (2) the acute, recurrent injury associated with rechallenge;\(^{20,25}\) and (3) a possible attenuation of the syndrome by the combination of prednisone therapy and a change in brands of FVIII concentrate.

Ideally, liver tissue from this patient should be studied during an episode of hepatitis in an attempt to identify the morphological changes and specific, fixed antibodies on hepatocytes. In addition, serum specimens should be obtained for determination of non-A, non-B and A and B marker proteins. Unfortunately, sera are no longer available from any of the previous episodes. Such studies will be performed if another episode of hepatitis occurs. In summary we suggest that an immune (allergic) mechanism should be considered in the differential diagnosis of FVIII-associated hepatitis in hemophiliacs.

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