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Acute Hepatitis Non-A, Non-B following Administration of Factor VIII Concentrates

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Abstract. A retrospective survey on clinical hepatitis in patients with bleeding disorders was performed. Nine episodes of hepatitis non-A, non-B occurred in 8 out of 20 patients (40%) with mild hemophilia A or von Willebrand's disease, who had been treated with commercial factor VIII concentrates. Only two episodes of hepatitis B occurred during the study period. The non-A, non-B attack rate after the first treatment was 40% with factor VIII concentrate obtained from large plasma pools (≈2,000 donors) including professional plasma donors as compared to 8% after treatment with factor VIII concentrate obtained from smaller (100–250 donors) plasma pools from Scandinavian donors.

Introduction

Viral hepatitis is a well-known complication of the treatment of patients with hemophilia. An increasing number of acute hepatitis cases, especially in patients with mild hemophilia, was seen after the introduction of freeze-dried coagulation factor concentrates from large plasma pools [2, 9]. Furthermore, development of chronic liver disease has been documented in multitransfused hemophiliacs during the last few years [10, 12, 13, 16]. It has been suggested that besides hepatitis B, other viruses as well may cause hepatitis in hemophiliacs [1]. After the development of serological methods to diagnose hepatitis A, it has been found that hepatitis non-A, non-B viruses are responsible for the non-B hepatitis cases [7].

In spite of very sensitive screening methods for hepatitis B surface antigen (HBsAg) in the selection of blood and plasma donors, hepatitis B still occurs after blood transfusion. It is not clear though, whether all these cases are due to blood transfusions or some are hospital acquired [1]. However, today non-A, non-B hepatitis is the major type of posttransfusion hepatitis [1, 3]. A similar trend has been noted for hepatitis following coagulation factor therapy [2].

The present retrospective study includes hepatitis cases occurring in a Hemophiliac

Center during 1974–June 1980. Serological methods have been used to diagnose hepatitis A and B and hepatitis non-A, non-B by exclusion of these hepatitis types. The occurrence of non-A, non-B hepatitis has been related to the type and the amount of factor VIII preparations used in the substitution therapy.

Material and Methods

Patients

The study population includes patients who were registered at the Coagulation Laboratory, Sahlgren's Hospital, Gothenburg, Sweden, during January 1974–June 1980. 37 patients with hemophilia A (13 with severe, 6 with moderate and 18 with mild hemophilia, including 2 carriers of the hemophilia gene) aged 13–71 years (mean 39 years), and 29 patients with von Willebrand's disease, 14–71 years of age (mean 43 years) were registered.

All patients were asked to answer a mailed questionnaire including questions on replacement therapy, symptoms typical for acute viral hepatitis and hospital stay. 60 out of 66 patients answered the questionnaire. Hospital journals were thereafter reviewed. Most of the hepatitis patients were hospitalized at the Department of Infectious Diseases, East Hospital, Gothenburg, Sweden.

The diagnosis of acute viral hepatitis was based on a typical history, symptoms and raised alanine aminotransferases in serum (at least five times the upper normal level). Antibodies to hepatitis A virus (anti-HAV) was determined by radioimmunoassay (HAVAB, Abbott Laboratories) and anti-HAV of IgM class was analyzed in acute phase serum samples on anti-HAV-positive samples [5]. Hepatitis B was diagnosed by the demonstration of HBsAg by Ausria II (Abbott) and antibody to the hepatitis B core antigen (anti-HBc) by Corab (Abbott). Immunofluorescence was used to detect IgM antibodies to cytomegalovirus [6] and the ox cell hemolysin test to detect heterophile antibodies to exclude Epstein-Barr virus infection [14].

Three commercial brands of factor VIII concentrate were used during the study period. Brand I was registered in 1967, is produced from Scandinavian volunteer blood donors (100–250 donors/batch), and was the most widely used preparation. Only brand I can be used as specific therapy in patients with von Willebrand's disease [15]. Since 1975, brand II, which is prepared from plasma pools up to 2,000 donors, including professional blood donors, has been used in parallel to brand I. Brand III was recently introduced into the therapeutic programme and is comparable with brand II regarding the size of the plasma pool and the type of donors used.

Results

Nine hepatitis non-A, non-B episodes were diagnosed during the study period (table I). Brand III was not involved in any case of non-A, non-B hepatitis. During the period 2 patients contracted acute hepatitis B after treatment with brands II and III, respectively. Hepatitis non-A, non-B occurred only in patients with either mild hemophilia A or von Willebrand's disease. 20 out of 47 patients registered with these diseases had been treated with factor VIII concentrate during the study period. 8 out of a total of 20 treated patients developed hepatitis non-A, non-B. 1 patient experienced two episodes of

Table I. Number of hepatitis non-A, non-B episodes following administration of two commercial brands (I, II) of factor VIII concentrate

Year	Commercial brands		
	I	II	I+II
1974–75	1	0	1
1976–77	1	1	0
1978–79	1	3	0
1980	0	1	0
	3	5	1

hepatitis non-A, non-B while another patient had non-A, non-B hepatitis followed by hepatitis B 3 years later.

The amount of factor VIII given to each patient varied between 1,000 and 10,400 U. Five episodes of hepatitis non-A, non-B occurred after the first treatment with factor VIII concentrate. 4 of the 5 patients developing non-A, non-B hepatitis after their first factor VIII treatment received factor VIII of brand II.

The patient who developed hepatitis non-A, non-B following treatment with brands I and II at the same time, had been treated with brand I twice before this actual treatment. The hepatitis non-A, non-B attack rate after the first treatment with factor VIII was 8% (1/13) with brand I and 40% (4/10) with brand II. No patient received therapy more than three times before development of hepatitis non-A, non-B.

In table II the total number of treatments given with brands I and II are related to the number of hepatitis non-A, non-episodes. It is seen that hepatitis following factor VIII treatment with brand II was found more frequently.

The mean incubation period was 5.6 weeks (range 2.5–9 weeks). Chronic liver disease developed in 3 patients. Prolonged symptoms justified that a biopsy was performed in 1 of these patients and the liver morphology was consistent with chronic aggressive hepatitis with slight cirrhosis [3].

Table II. Number of treatments with factor VIII concentrate and occurrence of hepatitis non-A, non-B in 20 patients with mild hemophilia A or von Willebrand's disease

Commercial brand of factor VIII	Number of treatments	Number of hepatitis non-A, non-B	%
I	21	4[1]	19
II	12	5	42

[1] 3 patients received supplementary therapy: (1) 1,500 U of brand II; (2) 3 U of blood; (3) 2,000 ml plasma.

Discussion

Today, non-A, non-B hepatitis has by far outnumbered hepatitis B as posttransfusion hepatitis. However, most cases of posttransfusion hepatitis non-A, non-B are asymptomatic. In spite of this being a retrospective study including clinical cases only, hepatitis non-A, non-B was almost five times as common as hepatitis B.

In the present study, only patients with either mild hemophilia A or von Willebrand's disease with a low need for replacement therapy fulfilled the criteria of acute viral hepatitis. A similar trend has been observed earlier [9]. Non-A, non-B hepatitis was seen in 5 patients who had never received any kind of factor VIII therapy before the actual episode. Four of these five episodes occurred after treatment with brand II. Furthermore, one non-A, non-B episode occurred when brand II, together with brand I, was given for the first time to a patient previously treated with brand I without complications.

A trend towards fewer cases on non-A, non-B hepatitis following therapy with brand I produced from a relatively smaller pool of volunteer donors from the Scandinavian countries was seen (table II). This was

most evident in the high hepatitis attack rate at first time treatment with brand II compared to brand I. Attack rates for different batches of the two brands, as demonstrated by *Craske* et al. [2], could not be given since the batch numbers of brand II were not known. However, it seems likely that different infectious batches were used, since about 10–15 different batches of this brand are imported by Sweden annually. Moreover, the cases were distributed without any tendency of clustering.

It is evident that the risk of transmitting hepatitis non-A, non-B is high with factor VIII preparations obtained from large plasma pools. Many authors therefore have advocated against the use of factor VIII prepared from large plasma pools and advised the use of preparations obtained from small plasma pools [8]. However, this has practical drawbacks in the treatment of patients with severe hemophilia and in major surgery on patients with mild hemophilia. But since the treatment of patients with mild bleeding disorders is so frequently followed by non-A, non-B hepatitis, often progressing to chronic liver disease, we agree that the policy to use factor VIII obtained from large plasma pools, should be restrictive in these cases. Hopefully, serological methods to diagnose non-A, non-B hepatitis soon will become more substantial than just promising reports. Continued work on virus inactivation or removal also has high priority.

Addendum

Since the end of the survey period, two cases of hepatitis non-A, non-B following treatment with factor VIII of brand III – which is comparable to brand II – have been diagnosed. One of these patients had never been treated with plasma or factor VIII concentrate before.

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