The epidemiology of Factor VIII and IX-associated hepatitis in the UK

J. Craig

Public Health Laboratory, Withington Hospital

Since 1969 the Oxford Haemophilia Centre on behalf of the UK Haemophilia Centre Directors has collected information about the incidence of jaundice after transfusion of Factor VIII and IX. The mainstay of treatment of haemophiliacs before 1974 was cryoprecipitate made from plasma obtained from UK volunteer blood donors, where each bag is made from one or two donations. This was supplemented by freeze-dried intermediate NHS Factor VIII and Factor IX prepared from UK volunteer blood donors.

Table 1: Jaundice in haemophiliac patients in the United Kingdom

<table>
<thead>
<tr>
<th>Year</th>
<th>Treated patients</th>
<th>No. of cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969</td>
<td>1048</td>
<td>19</td>
<td>1.81</td>
</tr>
<tr>
<td>1970</td>
<td>1041</td>
<td>25</td>
<td>2.40</td>
</tr>
<tr>
<td>1971</td>
<td>1143</td>
<td>22</td>
<td>1.92</td>
</tr>
<tr>
<td>1972</td>
<td>1191</td>
<td>17</td>
<td>1.42</td>
</tr>
<tr>
<td>1973</td>
<td>1124</td>
<td>26</td>
<td>2.31</td>
</tr>
<tr>
<td>1974</td>
<td>1634</td>
<td>85 (101)</td>
<td>5.20 (6.18)</td>
</tr>
<tr>
<td>1975</td>
<td>1609</td>
<td>42 (51)</td>
<td>2.61 (3.17)</td>
</tr>
<tr>
<td>1976</td>
<td>1886</td>
<td>56 (61)</td>
<td>2.97 (3.24)</td>
</tr>
<tr>
<td>1977</td>
<td>1968</td>
<td>50 (54)</td>
<td>2.54 (2.74)</td>
</tr>
<tr>
<td>1978</td>
<td>2039</td>
<td>41 (47)</td>
<td>2.01 (2.30)</td>
</tr>
<tr>
<td>1979</td>
<td>1935</td>
<td>33 (40)</td>
<td>1.70 (2.06)</td>
</tr>
</tbody>
</table>
In response to the increased demand for Factor VIII, commercial freeze-dried Factor VIII was imported from Europe and the USA to supplement NHS supplies. This was associated with an increase in the incidence of overt hepatitis from 2.31% in 1973 to 5.2% in 1974 (Table 1). Further studies showed in 1974–5 an attack rate of 17% in patients first treated with US commercial concentrate. Two types of hepatitis were observed: hepatitis B and what has since been shown to be non-A, non-B hepatitis with an incubation period of 6–70 days (mean 30.2 days)²,³.

In 1976, three further brands of Factor VIII were licensed in the UK (Table 1). There are now six brands in use. Four brands are manufactured in the USA from large pools of plasma (2–6000 litres) obtained by plasmapheresis of paid donors. These are high purity Factor VIII made by modifications of the PEC/glycine buffer fractionation method⁵. The fifth brand is manufactured in Austria and is an intermediate type of Factor VIII. The sixth product is NHS Intermediate concentrate prepared from plasma obtained from single donations of 200 ml each from UK volunteer donors. This means that the pool size of NHS Factor VIII may be larger (3500 donations per batch) than some batches of commercial factor where several litres of plasma is obtained by repeated plasmapheresis of one donor over a period of several weeks. This gives an advantage to commercial concentrate, and allows the use of large batches while keeping the number of donations per batch to a minimum. We do not know how this will affect the relative incidence of hepatitis associated with commercial Factor VIII compared with NHS concentrate, particularly as with whole blood transfusions there are 4 to 10 times the incidence of hepatitis associated with blood obtained from commercial, compared with voluntary donations⁵.

**TYPES OF HEPATITIS**

Further observations have confirmed that two types of hepatitis are associated with transfusions of Factor VIII and IX. Table 2 summarises the data collected in the UK since 1974.

**Hepatitis B**

Despite the introduction of RIA screening of plasma donation for HBsAg in 1975, a significant amount of both symptomatic and asymptomatic hepatitis B still occurs associated with commercial and NHS Factor VIII transfusions⁶.
Table 2  Hepatitis B and non-B hepatitis related to factor VIII transfusions in the UK

<table>
<thead>
<tr>
<th>Year</th>
<th>Batches</th>
<th>Non-B hepatitis</th>
<th>Hepatitis B (overt)</th>
<th>Total hepatitis</th>
<th>Total transfused</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-5</td>
<td>Q-V (6)</td>
<td>45 (14.6%)</td>
<td>26 (8.4%)</td>
<td>62</td>
<td>308F*</td>
<td>Commercial</td>
</tr>
<tr>
<td>1975</td>
<td>W-Z4 (7)</td>
<td>10 (7.4%)</td>
<td>2 (1.5%)</td>
<td>12</td>
<td>136F</td>
<td>Commercial</td>
</tr>
<tr>
<td>1975-6</td>
<td>K1-K12</td>
<td>13 (10.98)</td>
<td>4 (3.48%)</td>
<td>17</td>
<td>119F</td>
<td>Commercial</td>
</tr>
<tr>
<td>1977</td>
<td>NS</td>
<td>33 (1.68)</td>
<td>17 (0.56)</td>
<td>50 (2.54)</td>
<td>196BA**</td>
<td>All</td>
</tr>
<tr>
<td>1978</td>
<td>NS</td>
<td>34 (1.66)</td>
<td>8 (0.39)</td>
<td>47 (2.01)</td>
<td>2039A</td>
<td>All</td>
</tr>
<tr>
<td>1979</td>
<td>NS</td>
<td>29 (1.49)</td>
<td>4 (0.20)</td>
<td>33 (1.7)</td>
<td>1935A</td>
<td>All</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>164</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*F - first transfused  
**A - all transfused

Table 3  Prevalence of hepatitis B antibody Anti-HB<sub>c</sub> and Anti-HB<sub>c</sub>

in Oxford haemophiliacs

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Product transfused</th>
<th>Anti-HB&lt;sub&gt;c&lt;/sub&gt; or Anti-HB&lt;sub&gt;c&lt;/sub&gt; and Anti-HB&lt;sub&gt;c&lt;/sub&gt; positive</th>
<th>Anti-HB&lt;sub&gt;c&lt;/sub&gt; negative</th>
<th>HB Ag carriers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia 1A†</td>
<td>NHS + commercial VIII concentrate</td>
<td>112 (86%)</td>
<td>8 (6.0%)</td>
<td>3 (2.3%)</td>
<td>130</td>
</tr>
<tr>
<td>Severe*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia 1A†</td>
<td>Blood or cryoprecipitate</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Mild*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christmas disease</td>
<td>NHS IX</td>
<td>15 (88%)</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

* Severity of coagulation defect
† 7/130 patients with doubtful antibody status had antibody passively acquired from transfused concentrate
‡ 'Ausab' RIA Positive ratio > 20  
  Negative ratio < 3.0  
  Doubtful ratio < 20 and > 3.0
  Anti-HB<sub>c</sub> 'Corab' RIA
  □ 1/16 patients with doubtful antibody status
Table 3 shows the results of a survey carried out at the Oxford Haemophilia Centre of the prevalence of hepatitis B surface (anti-HBs) and core (anti-HBc) antibodies in different groups of patients by an immunosassay (RIA). A positive result is obtained from the ratio:

\[
\begin{align*}
\text{counts per minute in the test serum} \\
\text{counts per minute in the negative control serum}
\end{align*}
\]

A positive result was taken to be a ratio of > 20. Values below this may be due to passively acquired antibody from transfusions of factor VIII or IX (< 20 > 3.0). Ratios < 3.0 were considered to be negative (AUSAB RIA test - Abbott Laboratories Ltd.).

The results indicate that:

1) 75-80% of patients with severe Factor VIII or IX deficiency are anti-HBc positive, and are therefore immune to reinfection.

2) The proportion of carriers of hepatitis B virus (HBV) (3/130 or 2.3%) is no higher than in non-haemophiliacs with a similar exposure to HBV. Therefore, chronic hepatitis associated with HBV infection is not a major cause of chronic liver disease in British haemophiliacs.

3) Infection with HBV is highly correlated with the use of large plasma concentrate, both NHS and commercial. Most of these patients started treatment before RIA testing of donations for fractionation of plasma was introduced in 1975. Prospective studies of patients at Oxford after first transfusion of concentrate suggest that the attack rate for hepatitis B may have declined markedly, e.g. two out of eight patients (25%) showed serological evidence of symptomless hepatitis B infection after transfusions of up to 5000 Factor VIII units. Prior to 1975 the rate was probably 80-90%.

4) Many haemophiliacs with severe coagulation defect are exposed to hepatitis B infection before the age of 10 years. A high proportion of infection in young children is symptomless, as few give a history of symptomatic illness compatible with hepatitis B.
5) Patients with mild coagulation defects (VIII > 2%) often do not require regular Factor VIII therapy and only require concentrate to cover an operation or other major accident. Thus they do not receive treatment with concentrate until they are 30–40 years old when undergoing an operation or other procedure. They are then more likely to suffer from symptomatic hepatitis B than if they had contracted it as a child.

Non-A, Non-B Hepatitis

The acute illness is clinically mild with an incubation period of 6–70 days and is clinically indistinguishable from hepatitis A and B. Of a total of 136 cases where transfusion history was known, 103 have been associated with first transfusion of Factor VIII or IX concentrate. Only seven cases have been associated with transfusions of cryoprecipitate. Each patient had received cryoprecipitate from between 50 and 100 plasma donations in the 6 months prior to the onset of acute hepatitis. This suggests a low contamination ratio for cryoprecipitate made from UK volunteer donors for non-A, non-B hepatitis. Secondary symptomatic cases have not been reported in household contacts in contrast to hepatitis B, where six secondary cases have occurred since 1974.

We have recently published evidence, based on the occurrence of multiple attacks of hepatitis in haemophiliacs, in favour of the existence of at least two types of non-A, non-B hepatitis associated with transfusions of Factor VIII. One type is associated with US sourced commercial products. The second is associated with NHS Factor VIII and European commercial products. This association of different serotypes with different brands of Factor VIII is probably related to the different fractionation process used in the preparation of US commercial Factor VIII compared with NHS Factor VIII and European. The US products are made from modifications of the PEG/glycine fractionation method.

The early reported cases associated with US commercial concentrates had a high attack rate (14.6%). These were patients receiving their first transfusion of concentrate. However, the current cumulative attack rate is almost 1.7% of the total patients treated in 1979 in the UK (Table 2). Studies of patients receiving first transfusions of concentrate suggest that the attack rate for non-A, non-B hepatitis has remained unchanged since 1974. This is in marked contrast to the risk of
contracting hepatitis B which has fallen since the introduction of plasma donations for HBsAg.

Symptomless Non-A, Non-B Hepatitis

It was shown in a recent publication⁷ that a patient was 70% more likely to contract symptomatic non-A, non-B hepatitis with first batch of concentrate he received than after a second or subsequent batch⁷. This suggested that symptomless patients were protected from contracting hepatitis after transfusion of second or subsequent batches of concentrate due to the acquisition of immunity from a symptomless infection associated with the first batch of concentrate transfused. Recent evidence suggests that the overall attack rate including symptomless infection about 80-90% with the first batch of concentrate received⁶,⁸.

Table 4. Factor VIII associated hepatitis: commercial and NHS brands. Attack rates in patients receiving one product in a treatment year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Brand</th>
<th>Cases of hepatitis</th>
<th></th>
<th></th>
<th></th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-B</td>
<td>Overt</td>
<td>Total overt hepatitis</td>
<td>Total transfused</td>
<td>Comm/NHS Non-B B</td>
</tr>
<tr>
<td>1977</td>
<td>*Comm</td>
<td>3 (2.67)</td>
<td>2 (1.78)</td>
<td>5 (4.46)</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*NHS</td>
<td>1 (0.56)</td>
<td>4 (2.23)</td>
<td>5 (2.79)</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>Comm</td>
<td>14 (7.7)</td>
<td>1 (0.5)</td>
<td>15 (8.3)</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHS</td>
<td>1 (0.39)</td>
<td>2 (0.63)</td>
<td>3 (0.96)</td>
<td>313</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Comm</td>
<td>10 (6.30)</td>
<td>1 (0.63)</td>
<td>11 (6.96)</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHS</td>
<td>1 (0.29)</td>
<td>0</td>
<td>1 (0.29)</td>
<td>342</td>
<td></td>
</tr>
</tbody>
</table>

* Comm - Commercial concentrate
* NHS - National Health Service (Intermediate) factor VIII concentrate
* n/s - not significant

Figures in brackets equal percentages
The attack rates for symptomatic hepatitis for patients treated with one brand of concentrate in any year suggest that there is an increased risk from commercial Factor VIII compared with NHS Factor VIII (see Table 4), but no firm conclusion can be drawn until prospective studies have been carried out.

Complications

Most cases of non-A, non-B hepatitis are mild illnesses. Six cases have been reported as 'severe'. Two patients have died in the acute stage of the disease, but there were complicating factors in both instances.

Acute Fulminating Hepatitis

This has not been reported in our survey, but occurred after transfusions of Factor IX to non-jaundiced patients with chronic liver disease not associated with viral hepatitis. The Factor IX was used to achieve normal clotting factor levels prior to liver biopsy or other operative procedure. In one episode, three out of four patients who contracted non-A, non-B hepatitis died of acute fulminating hepatitis. The use of Factor IX concentrate is, therefore, strongly contraindicated in non-jaundiced patients until a means is found of rendering these products safe from the risk of acute hepatitis.

Chronic Liver Disease

About 25-40% of haemophiliacs on regular Factor VIII therapy have persistently elevated serum aminotransferase levels for periods of at least one year. Most of these patients are symptomless. However, a few have clinical features suggestive of chronic liver disease, but the ethical problems associated with the indications for liver biopsy have meant that few patients have so far undergone this procedure. About 40 patients have undergone biopsy in the UK and approximately 50% of these have histological evidence of chronic persistent hepatitis. Other patients showed evidence of chronic liver disease or cirrhosis. The histological changes showed no correlation with the degree of disturbance of the serum enzyme levels. The only common factor was regular treatment with Factor VIII concentrate. Most of the patients in this group are children or young adults, though the age range at Oxford is 6-70 years. It seems likely that some patients will develop severe chronic liver disease over the next 10 years. Further data relating to problems will be given in later papers in this Symposium. There is no evidence that household contacts of haemophiliacs are liable to develop chronic liver disease.
Since less than 5% of British haemophiliacs are carriers of HBV, it is likely that most of the chronic hepatitis is a sequel to infection with one or more non-B hepatitis virus(es). A carrier state similar to that for hepatitis B has been recently shown to exist for at least 6 years \(^{15}\). There is as yet no evidence that any other factor is involved, such as hypersensitivity to components in the transfused concentrate or constant re-exposure to chemicals in the concentrate. One patient suffered from five successive attacks of acute hepatitis following five successive transfusion episodes, several months apart \(^{16}\). Each episode was followed by the liver function tests returning to normal. The last episode was partially alleviated with steroids. The authors suggested that the patient conceivably suffered from hypersensitivity to a component in the transfused concentrate. These features are in marked contrast to those associated with viral hepatitis.

There is, therefore, a high risk from the use of Factor VIII or IX concentrate that the patient will contract non-A, non-B hepatitis, or co-infection with resultant chronic hepatitis, together with a smaller risk of hepatitis B. Most severe haemophiliacs in the UK have now been exposed to these viruses. Until tests are available for these agents, the possibility of using small pool concentrate or a wider use of cryoprecipitate should be considered for patients with mild coagulation defects requiring treatment. Cover surgery or other major treatment. These patients are infrequent treated and run a high risk of transfusion hepatitis if concentrate is used for the first time.

REFERENCES


13. Lessesne, H.R., Morgan, J.E., Blatt, P.M., Webster, W.P., an
Discussion

I was not quite sure about the difference in incidence of hepatitis between the commercial concentrates and the NHS concentrate.

The problem is that it looks as if there is a higher incidence in overt cases, but the difficulty is that in the population we have studied there are so many patients who have treatment before. That is why I was a bit guarded about interpretation.

This would provide evidence, as you suggest, there might be a number of different agents responsible for causing hepatitis, and it might be explicable on that basis. Have you seen patients who have been treated with the NHS concentrate and subsequently had the commercial and then developed overt hepatitis?
Yes. This was actually reported 2 years ago in the Lancet. We have a group of about 20 patients who had multiple attacks and the evidence may be interpreted as suggesting that these patients experienced 2 attacks of non-A, non-B hepatitis, and that they could have experienced 3 agents at least. Interestingly enough the incubation periods seemed to all be of this short type. One other thing, which has been reported recently, has been a case where a patient had 5 episodes of jaundice after successive transfusions of concentrate, in which this was thought to be related to allergy to some product in the Factor VIII. The interesting feature of this was that the incubation period in successive exposures got less and less until at the final exposure the incubation period was about 3 days. In each case the liver function test, returned to normal after a month or two, so that this would seem to be a different type of hepatitis to the one we have been describing today. When the report came up I looked at the incubation periods in our multiple cases and the second episode of hepatitis did not, in most cases, have a shorter incubation period than the first. Thus I do not think our repeated cases can be explained on allergy.

I suppose the other possibility is that in non-A, non-E hepatitis where there are fluctuations in liver function tests there may just be a coincidental change in transaminase levels.

That is true, but these cases all had overt jaundice. These were mostly mildly affected patients, and in a quarter of the cases liver function tests had returned to normal. We do not seem to see this very often with severely affected ones. This may just be that they get very heavy exposure, and therefore they perhaps get infections very close together. We also looked at the incidence of hepatitis-A antibody in haemophiliacs at Oxford and there is no correlation with exposure to concentrates at all. The incidence of antibodies is exactly what we would expect from a comparable group of non-haemophiliacs in Oxford who experienced hepatitis-A infection by other routes.

We have two reports of hepatitis-A in haemophilia-B patients a Oxford where it seems just remotely possible that they could have acquired it from concentrate. We are looking into this possibility because we do
seem to have a cluster. But whether this is related to the concentration remains to be seen but it is theoretically possible.

As I understand it, non-A, non-B causes chronic hepatitis. They keep getting it and they keep on with the abnormalities in the liver function tests. How can this be squared with the explanation regarding the severely affected patients that have been exposed and have become infected?

Dr. White: The point is that being an infective disease, it needs only one exposure to get infected. After exposure to this infection the patient presumably gets a chronic inflammatory process in the liver, which is where the persistence, as evidenced by the abnormal liver function tests, addition there is better evidence which will be demonstrated by the people who will describe the abnormalities of the liver biopsy.

How can this be squared with the severe cases who do not seem to have it?

They do not get a fresh attack of jaundice. That is what I meant. We do not see fresh cases of overt non-A, non-B hepatitis in patients who have been transfused with so much concentrate that they have experienced all the possible infective agents present in this material.

Have they still got abnormal liver function?

A high proportion of them have. Some of them get better within 6 months and some a year. One of the problems is length of time which is the normal lifespan of this infection? We do know, and it seems to be a bit longer than other types of hepatitis.

The difficulty is that one may be dealing with a pattern...
who has a background of chronic liver disease, and whether another attack of hepatitis or jaundice in that patient should be equated with a reinfection or an exacerbation of acute-on-chronic episodes presents a lot of problems.

There is a small amount of cases, which I have not described, where we get jaundice in patients who are considered to have chronic liver disease, and we do not know what it is due to; there are many possible causes. I have deliberately excluded these. It was only in two cases where the epidemiological evidence suggested that it was related to the transfusion episode and where the director concerned was convinced that the clinical symptoms would fit this syndrome. The confirmation of this is the constant number of incidents we get and the constant situation where it occurs.