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

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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[1]. 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

Year	Treated patients	No. of cases	Percent	
1969	1048	19	1.81	
1970	1041	25	2.40	
1971	1143	22	1.92	
1972	1191	17	1.42	
1973	1124	26	2.31	Commercial concentrates
1974	1634	85 (101)	5.20 (6.18)	first used
1975	1609	42 (51)	2.61 (3.17)	
1976	1886	56 (61)	2.97 (3.24)	Other commercial
1977	1968	50 (54)	2.54 (2.74)	concentrates
1978	2039	41 (47)	2.01 (2.30)	
1979	1935	33 (40)	1.70 (2.06)	

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In response to the increased demand for Factor VIII, commerci freeze dried Factor VIII was imported from Europe and the USA to supplem NHS supplies. This was associated with an increase in the incidence overt hepatitis from 2.31% in 1973 to 5.2% in 1974 (Table 1). Furth studies showed in 1974-5 an attack rate of 17% in patients first treated wi US commercial concentrate. Two types of hepatitis were observed; hepatit B and what has since been shown to be non-A, non-B hepatitis with incubation period of 6-70 days (mean 30.2 days)[2,3].

In 1976, three further brands of Factor VIII were licensed in t UK (Table 1). There are now six brands in use. Four bran manufactured in the USA from large pools of plasma (2-6000 litres) obtain by plasmapheresis of paid donors. These are high purity Factor VII made by modifications of the PEG/glycine buffer fractionation method[4]. fifth brand is manufactured in Austria and is an intermediate type of Fact VIII. The sixth product is NHS intermediate concentrate prepared fr plasma obtained from single donations of 200 ml each from UK volunte donors. This means that the pool size of NHS Factor VIII may be larg (3500 donations per batch) than some batches of commercial factor whe several litres of plasma is obtained by repeated plasmapheresis of one don over a period of several weeks. This gives an advantage to commerci concentrate, and allows the use of large batches while keeping the numb of donations per batch to a minimum. We do not know how this will affe the relative incidence of hepatitis associated with commercial Factor VI compared with NHS concentrate, particularly as with whole blo transfusions there are 4 to 10 times the incidence of hepatitis associat with blood obtained from commercial, compared with voluntary donations[5].

TYPES OF HEPATITIS

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

Hepatitis B

Despite the introduction of RIA screening of plasma donation f HB_sAg in 1975, a significant amount of both symptomatic and symptomle hepatitis B still occurs associated with commercial and NHS Factor VI transfusions[6].

Table 2 Hepatitis B and non-B hepatitis related to factor VIII transfusions in the UK

Year	Batches	Non-B hepatitis	Hepatitis B (overt)	Total hepatitis	Total transfused	Product
1974-5	Q-V (6)	45 (14.6%)	26 (8.4%)	62	308F*	Commerci
1975	W-Z4(7)	10 (7.4%)	2 (1.5%)	12	136F	Commerci
1975-6	K1-K12	13 (10.9%)	4 (3.4%)	17	119F	Commerci
1977	NS	33 (1.68)	17 (0.56)	50 (2.54)	1968A**	All
1978	NS	34 (1.66)	8 (0.39)	47 (2.01)	2039A	All
1979	NS	29 (1.49)	4 (0.20)	33 (1.7)	1935A	All
TOTAL		164	61			

*F - first transfused
**A - all transfused

Table 3 Prevalence of hepatitis B antibody Anti-HB_s and Anti-HB_c in Oxford haemophiliacs

Treatment group	Product transfused	Anti-HB_c or Anti-HB_s positive±	Anti-HB_c and Anti-HB_s negative	HB_sAg carriers	Total
Haemophilia 'A' Severe*	NHS + commercial VIII concentrate	112 (86%)	8 (6.0%)	3 (2.3%)	130 #
Haemophilia 'A' Mild*	Blood or cryoprecipitate	0	17	0	17
Christmas disease	NHS IX concentrate	15 (88%)	0	0	16 <>

* 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_c 'Corab' RIA
<> 1/16 patients with doubtful antibody status

Table 3 shows the results of a survey carried out at the Oxf Haemophilia Centre of the prevalence of hepatitis B surface (anti-HB_s) core (anti-HB_c) antibodies in different groups of patients by ra immunoassay (RIA). A positive result is obtained from the ratio:

$$\frac{\text{counts per minute in the test serum}}{\text{counts per minute in the negative control serum}}$$

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

The results indicate that -

1) 75-80% of patients with severe Factor VIII or IX deficiency are anti-HB_s 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 po concentrate, both NHS and commercial. Most of these patients started treatment before RIA testing of donations for fractionatic of plasma was introduced in 1975. Prospective studies of patien at Oxford after first transfusion of concentrate suggest that the attack rate for hepatitis B may have declined markedly, e.g. tw out of eight patients (25%) showed serological evidence of symptomless hepatitis B infection after transfusions of up to 500 Factor VIII units. Prior to 1975 the rate was probably 80-90%[3].

4) Many haemophiliacs with severe coagulation defect are exposed to hepatitis B infection before the age of 10 years. A high proport 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 symtomatic 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 138 cases where transfusion history was known, 103 have been associated with first transfusion of Factor VIII or IX concentrate[6]. 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 actue 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[7], 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[4].

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[6]. This is in marked contrast to the risk of

contracting hepatitis B which has fallen since the introduction of l screening of plasma donations for HB_sAg.

Symptomless Non-A, Non-B Hepatitis

It was shown in a recent publication[7] that a patient was times more likely to contract symptomatic non-A, non-B hepatitis with first batch of concentrate he received than after a second or subsequ batch[7]. This suggested that symptomless patients were protected f contracting hepatitis after transfusion of second or subsequent batches concentrate due to the acquisition of immunity from a symptomless infect associated with the first batch of concentrate transfused. Recent evide suggests that the overall attack rate including symptomless infection about 80-90% with the first batch of concentrate received[6,8].

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

Year	Brand	Cases of hepatitis Non-B (overt)	Overt B	Total overt hepatitis	Total transfused	Ratio Comm/NHS Non-B	B
1977	*Comm	3 (2.67)	2 (1.78)	5 (4.46)	112)		
					)	4.76	0.
	*NHS	1 (0.56)	4 (2.23)	5 (2.79)	179)		
1978	Comm	14 (7.7)	1 (0.5)	15 (8.3)	180)		
					)	19.7	0.
	NHS	1 (0.39)	2 (0.63)	3 (0.96)	313)		
1979	Comm	10 (6.30)	1 (0.63)	11 (6.96)	158)		
					)	21.73	*r
	NHS	1 (0.29)	0	1 (0.29)	342)		

* Comm - Commercial concentrate
* NHS - National Health Service (Intermediate) factor VIII concentrat
* 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 occured after transfusions of Factor IX to non-haemophiliac patients with chronic liver disease not associated with viral hepatitis[9,10]. The Factor IX was used to achieve normal clotting factor levels prior to liver biopsy or other operative procedure. In one episode[9], 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-haemophiliac 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[11,12]. 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[13,14]. 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 is likely that most of the chronic hepatitis is a sequel to infection with r non-B hepatitis virus(es). A carrier state similar to that for hepatiti has been recently shown to exist for at least 6 years[15]. There is as ye evidence that any other factor is involved, such as hypersensitivity components in the transfused concentrate or constant re-exposure to t chemicals in the concentrate. One patient suffered from five succes attacks of acute hepatitis following five successive transfusion epis several months apart[16]. Each episode was followed by the liver func tests returning to normal. The last episode was partially alleviated treatment with steroids. The authors suggested that the patient concer suffered from hypersensitivity to a component in the transfused concentr These features are in marked contrast to those associated with viral hep

There is, therefore, a high risk from the use of Factor VIII o IX concentrate that the patient will contract non-A, non-B hepatitis, ar 20-30% chance of resultant chronic hepatitis, together with a smaller ris hepatitis B. Most severe haemophiliacs in the UK have now been exp to these viruses. Until tests are available for these agents, the possib of using small pool concentrate or a wider use of cryoprecipitate shoul considered for patients with mild coagulation defects requiring treatmen cover surgery or other major treatment. These patients are infreque treated and run a high risk of transfusion hepatitis if concentrate is u for the first time.

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Discussion

I was not quite sure about the difference in incid of hepatitis between the commercial concentrates and the NHS concentrat

The problem is that it looks as if there is a n 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 commerical and then developed overt hepatitis?

[illegible]. 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-B 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 at 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 concentra remains to be seen but it is theoretically possible.

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

Dr. _____ The point is that being an infective disease, it nee one exposure to get infected. After exposure to this infection the patie presumably gets a chronic inflammatory process in the liver, which is wi he gets persistence, as evidenced by the abnormal liver function tests. addition there is better evidence which will be demonstrated by the peo who will describe the abnormalities of the liver biopsy.

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

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

_____ : Have they still got abnormal liver funtion?

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 pati

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.