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REPORT OF THE HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY 1979

The working party has held three meetings during the year. Most of the business consisted of the organisation of projects related to the hepatitis surveillance programme and to the study of chronic liver disease in patients at the Oxford Haemophilia Centre.

The working party consists of:-
Dr J Craske - (Chairman)
Miss R D J Spooner
Dr Howard Davies - Director of the Edinburgh Haemophilia Centre
Dr Drummond Ellis - Blood Products Laboratory Lister Institute Elstree Herts
Dr Joan Trowell - Lecturer in medicine John Radcliffe Hospital Oxford
Dr Susanta Ghosh - Research Fellow in Hepatitis Oxford Haemophilia Centre

Dr Davies retired from his post as Director of the Haemophilia Centre at Edinburgh Royal Infirmary on October 1st 1979. He has contributed a great deal of his time and enthusiasm to the working party since it was formed. I have asked him to remain as a member as his advise and encouragement will be invaluable for our work in future.

We have felt the need for a further practicing clinician on the working party and therefore I have invited Dr Peter Kernoff, Co-Director of the Royal Free Hospital Haemophilia Centre, London, to serve on the working party and he has kindly accepted.

This year has seen the completion of the first year of the surveillance programme financed by a grant from the Department of Health and Social Security. This is part of a three year programme. The second part of this project consists of an investigation for evidence of chronic liver disease in haemophiliacs on long term factor VIII therapy. This is being carried out at Oxford by Dr Ghosh and Dr Trowell, under the direction of Dr Rizza.

HEPATITIS SURVEILLANCE - (Non-A, Non-B = N/A, N/B)

The prevalence of hepatitis in 1978 and 1979 has had about the same level as that observed in 1976-7. There has been an increase in the proportion of cases of N/A, N/B hepatitis reported in patients with mild disease receiving concentrate for the first time have been to cover operation. In table one the proportion of severe and mild haemophiliacs who contracted N/B hepatitis related to NHS and commercial concentrate in 1974-5, is compared with those reported in 1978. The observed increase in mild haemophiliacs contracting hepatitis is probably due to the fact that most severe haemophiliacs have already been exposed to viruses present in all brands of concentrate and are therefore immune to re-infection. Patients with mild disease have not so been exposed; therefore there is no evidence to suggest that the contamination rate of different brands or batches of concentrate with N/A, N/B viruses has diminished. There is some evidence to suggest that the contamination rate with hepatitis B virus may have dropped. Table two relates haemophilia associated hepatitis B to the results of Radioimmunoassay (RIA) screen in batches of concentrate for HB_sAg.

Since September 1975, a considerable number of batches of NHS commercial concentrate associated with cases of hepatitis B have been screened in Dr Dane's laboratory in London and all have proved negative for HB_sAg although (RIA) techniques have since improved in sensitivity. However, cases of hepatitis B are still regularly imported, and most severe haemophiliacs are immune to hepatitis B.

112 out of 122 patients have so far been found at Oxford to have evidence of past infection with hepatitis B virus; this included three carriers of HB_sAg. Some of the anti-HB_s detected may have been due to antibodies passively aquired from transfusion concentrate. Fig. 3, apendix 1, prepared by Dr Ghosh shows the relationship of the results of a positive RIA test for anti HB_s and the time in days between the last transfusion of factor VIII and the collection of the serum specimen.

The RIA results are expressed as the ratio:-

$$\frac{\text{RIA Counts in Test Specimen of Serum}}{\text{Counts in Negative Control Specimen}}$$

The testing of repeat specimens may allow us to determine what proportion of antibody is passively aquired and how much is related to a secondary response to HB_sAg in the transfusion concentrate.

RELATIONSHIP OF HEPATITIS TO DIFFERENT BRANDS OF CONCENTRATE

The Directors will recall that they were asked to include in their Annual Report whether each patient had received one or more batches of each brand of concentrate in any treatment year. With the aid of the computer unit at the Oxford Area Health Authority (T), we have analysed the figures for 1977 and these are shown in table 3. The hepatitis attack rates for each brand of concentrate should be thought of as cumulative. i.e. The number of patients contracting hepatitis, related to a brand of concentrate, divided by the patients receiving that product in the treatment year. A variable proportion of these patients will have received these or other products in previous years, so that the longer a product is used the lower the cumulative attack rate will become. This is shown in table 4 for Hemofil.

The first exposure attack rate i.e. The number of acute hepatitis cases divided by the total first treated with any product, will be derived in 1978 by comparison with 1977 dates by deleting those patients who have previously received the same product in 1977, which they received in 1978, when calculating the first exposure attack rate. One obvious result for the 1977 data is a relatively high incidence of hepatitis B related to Factorate, compared with other products. It is likely that this result will be confirmed when the 1978 figures are analysed. Most of the cases in 1977 were related in one batch, but other implicated batches of factor have been reported for 1978.

Table 5 shows the relationship of the age of onset of cases of hepatitis for 1974-5 compared with those reported in 1977-8. The high prevalence of older patients with hepatitis is mainly due to these patients being first exposed to concentrate when undergoing an operation.

Analysis of cases coming to operation in the past eighteen months at Oxford shows that prior treatment with concentrate was the main factor which was associated with freedom from N/A, N/B hepatitis. Since May 1977, 72 operations requiring factor VIII cover were carried out. 57 of the patients involved had severe disease (less than 2% factor VIII) and one contracted N/A, N/B hepatitis. 15 patients with mild disease ($\geq$ 2% factor VIII) produced four cases of N/A, N/B hepatitis. After receiving concentrate, no cases of hepatitis B occurred.

MORTALITY

No further fatalities directly due to acute hepatitis have been reported. One patient had acute N/A, N/B hepatitis followed by persistent raised enzyme levels in 1978. He died by a retroperitoneal haemorrhage, post mortem was refused but it is possible that his hepatitis indirectly contributed to his death.

A further patient at Oxford who died of causes unrelated to liver disease was found on post mortem to have portal cirrhosis. He was HB_sAg negative. We will be interested in any further cases where specimens of post mortem liver can be obtained from haemophiliacs, to collect further evidence of the prevalence of chronic liver disease. The preliminary results of the patients at Oxford so far studied for evidence of chronic liver disease are given in apendix 1, which was compiled by Dr Ghosh. 70 out of 174 patients (40.2%) had persistent transaminitis but only 20 of these so far have been found to have clinical evidence suggestive of chronic liver disease. The main conclusions so far are that:-

1. Transaminitis is unrelated to current factor VIII therapy and the level of anti HB_s antibody.

2. Transaminitis is unrelated to a previous history of overt hepatitis.

This is supported by the observation that in 6 out of 7 cases of jaundiced patients observed at Oxford in the past year, the liver function tests quickly returned to normal after the acute attack. The seventh patient is considered to have suffered from jaundice related to his chronic liver disease and was not a case of acute hepatitis.

These results suggest that if transaminitis is related to viral hepatitis, the patients who become carriers and develop chronic liver disease will only contract mild or symptomless acute hepatitis, and the most overtly jaundiced patients will fully recover. This is supported by our observations of hepatitis B infections in haemophiliacs, but more information is needed to provide a large enough source of patients. Dr Dane has made similar observations in non-haemophiliac patients.

Early reports in the USA suggested that some acute cases of hepatitis B with jaundice, in some cases became carriers. In retrospect it is likely that many of thes may have been cases of acute N/B hepatitis occurring from carriers of hepatitis B virus which were hitherto unrecognised. At that time tests for other viruses were not available. We therefore propose that the working party should organise a follow-up of the cases of acute hepatitis B, notified to the Oxford Haemophilia Centre to see if the postulated relationship between jaundice and recovery of hepatitis is confirmed by further observations.

OTHER POSSIBLE CAUSES OF LIVER DIMENSION IN HAEMOPHILIACS

Alcohol Intoxication

6 of the 174 patients at Oxford have some dependence on alcohol. Two of these have been found to have transaminitis. However, our observations suggest that alcohol increased the severity of transaminitis, but that it is not a chief cause of the elevated enzymes in these two patients.

Direct Dependence

10 of the 174 patients have some dependence on analgesics, but none so far have been found to have Transaminitis.

Further Studies

We have based our initial assessment of enzyme levels on SGOT measurements as this is the routine test in use at Oxford. Within the next year each patient will be re-assessed using the SGPT test. This is known to be a more sensitive index of liver damage due to viral hepatitis in himans and experiments in chimpanzees.

EVIDENCE OF TWO TYPES OF NON-A, NON-B HEPATITIS

The observations recorded in the 1978 report were described in a letter published in the Lancet (1). Observations made since then have given additional evidence for the existence of two types of N/A, N/B hepatitis causing short incubation illness in haemophiliacs on factor VIII therapy. One is probably related to commercial concentrate originating from the USA, and the screen to NHS factor VIII, and Kryobulin.

PREVENTION OF VIRUS INFECTION

a) Hepatitis B Vaccine. As indicated in the 1978 report, one vaccine is at present undergoing trials in the USA, and priliminary results should be available in the summer of 1980. We are due to have further discussions with persons involved in this trial to see whether such a vaccine would be of value in haemophiliacs. There are, however, considerable difficulties to be overcome before this can be considered.

b) N/A, N/B Hepatitis. Collaborative experiments with the Bureau of Biologics in Washington are about to start. Similar experiments are being undertaken in collaboration with Professor Arie Zuckerman of the Department of Microbiology of the London School of Hygiene and Tropical Medicine. One group at the Communicable Disease Centre, Atlanta, Georgia, has published results suggesting that the N/A, N/B hepatitis associated with haemophilia, is due to small round particles (3). This work remains to be confirmed.

c) Hepatitis B in the Household Contacts of Haemophiliacs. During the past two years four cases of hepatitis B have occurred in household contacts of patients who contracted factor VIII or IX associated hepatitis B. Two of these secondary cases were members of the family who administered factor to the index case. We are carrying out a small survey of the incidence of hepatitis B antigen antibody in the relatives of patients treated at Oxford to try and establish a degree of risk to relatives of haemophiliacs of contracting hepatitis B. So far no cases of overt N/A, N/B hepatitis in household contacts of haemophiliacs have been reported in our survey.

d) Future Research. Several projects are in hand at Oxford to determine the value of various tests for the assessment of chronic liver disease in haemophiliacs.

A prospective study of factor VIII prepared for the Canadian Red Cross by Travenol Laboratories Inc. from volunteer blood donations in Canada has just started. This project has arisen out of a visit I made to Toronto. The protocol for the project was prepared by me at the request of the Canadian Red Cross. The second year of this project will use plasma fractionated by Cutter Labotatories, also from Canadian voluntary blood donors. The pool size used for each batch of concentrate is of the order of 10,000 donations. Our thanks are due to the directors of the Haemophilia Centres for their contribution to the continuing survey of hepatitis in haemophiliacs. We hope that in the next two years some pertinent answers and possible solutions to this problem may become evident as the work continues.

Dr D Craske
Chairman