Hepatitis

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1. Historical

The occurrence of jaundice after introduction of human plasma into the body was first noted well over 100 years ago in German shipyard workers who were vaccinated with a human lymph-derived vaccine and later further described during the Second World War in British soldiers inocculated using multi-shared syringes. In 1943, Beeson reviewed this information and described other patients suffering from what was then called "homologous serum jaundice". This condition was further reviewed by Spurling et al in 1964, who recognised the increased risk of pooling blood plasma for infusions into patients.

2. Hepatitis A

By 1972, two forms of hepatitis were recognised, hepatitis A with short incubation and normally transmitted via the faecal oral route. Longterm blood carriers of hepatitis A are very rare and transfusion of the condition was not thought a significant problem until the mid-1990s.

3. Hepatitis B

This form of hepatitis is the one described as haemologous serum jaundice by Besson and it has a long incubation period of up to six months and is termed hepatitis B as distinct from hepatitis A. In 1967, Blumberg and colleagues described the substance in the blood of Australian aborigines and noted that this was present in the blood of patients amongst others who had serum hepatitis. Antibodies to this substance were observed in haemophilic patients amongst others who had received multiple transfusions. Australia antigen was later identified as a component part of the virus of hepatitis B. Crude tests for Australia antigen were the precursors of the more sensitive screening tests for hepatitis B, which were eventually introduced during the late 1970s. Maycock, in 1972, reviewed the evidence then available and found that a certain proportion of persons who developed hepatitis B could actually be symptomless carriers capable of infecting others via the route of transfusion. It is also noteworthy that hepatitis B occurs naturally and later evidence showed that it could be sexually transmitted. It is more prevalent in Oriental than in European and North American populations. In the early 1970s it was appreciated that the prevalence of hepatitis B was increased both in drug addicts and in prison inmates.

4. Non-A non-B Hepatitis

In 1974 Prince et al first noted that a large proportion of post transfusion hepatitis patients did not have any evidence of the B hepatitis virus. They postulated that there could be other transfusion-transmitted hepatitis virus(es) Type C. In 1974 Alter and colleagues confirmed these findings and from then on the term "non-A non-B hepatitis" was used. There appeared to be several types of non-A non-B hepatitis; the type which has a short incubation period of 4-6 weeks and some which have a longer incubation period of up to 10-12 weeks (Craske 1978). The clinical picture of non-A non-B hepatitis compared to hepatitis B tends to be mild. Very frequently the infection is totally symptomless and may only be detected by blood tests of liver function. The most usual test is of a substance known as transaminase. A persistently raised transaminase known as ALT, used to be presumptive evidence of hepatitis in multi-transfused patients.

The risk that non-A non-B hepatitis could progress to chronic hepatitis was known in 1977 but the full significance of its effects was not appreciated, elaborated and investigated until the mid- to late-1980s. Chew et al described the isolation of a cDNA clone derived from a blood-bourne non-A non-B viral hepatitis genome in 1989. In the same journal they also described an assay for circulating antibodies to a major aetiological virus of human non-A non-B hepatitis. This test was described as the recombinant HCV "C100-3 antigen". This preparation was used as the HCV target antigen in the first generation anti-HCV Elisa assay. Although the assay was extensively evaluated, it was found to be relatively insensitive and not very specific. It gave both false positive and false negative results (Aach et al 1991). In that same year, Houghton et al described the molecular biology of the hepatitis C viruses. Their publication was in the liver journal, Hepatology, in 1991. The specific and accurate third generation tests were introduced in 1993 and thereafter using PCR genetic technology, it was possible to make a firm diagnosis of the presence of HCV antibody in a patient and also detect which of the six recognised genotypes had infected the patient.

5. Hepatitis D

Hepatitis D or that caused by the delta virus can only live in simbiosis with the hepatitis B virus and does not cause any disease in the absence of hepatitis B. However, if the delta virus coexists with hepatitis B, aggressive liver disease may result. However, delta virus infection is uncommon in British and American populations but is more prevalent in Italy. In the Northern Ireland Haemophilia Centre, only one patient contracted the delta virus subsequent to a previous asymptomatic infection with hepatitis B.

6. Hepatitis in Patients with Haemophilia A and B

Transfusion associated hepatitis was recognised with increasing frequency following the use of FFP and plasma derived concentrates, produced for the treatment of all types of haemophilia. The haemophilia physicians of the United Kingdom constantly addressed the problem from 1967 onwards, culminating in the establishment of the United Kingdom Haemophilia Directors Hepatitis Working Party. It was instituted in 1977 under the chairmanship of the virologist, Dr John Craske.

In the early 1970s, hepatitis B infection was giving rise to the greatest concern. Therefore, attention was directed towards the detection of asymptomatic hepatitis B in the apparently normal blood donor population. The first tests were relatively insensitive and only around 30% of cases of post transfusion hepatitis were estimated to be eliminated by the introduction of early testing. In 1972, mandatory testing for blood donors was introduced. Subsequently, a radioimmuno assay (RIA) was developed. It was more sensitive but had the disadvantage of producing false positive results – perhaps, at least an improvement over false negativity. The quest for more sensitive tests continued. However, it was felt that the risk of transmission of hepatitis B infection for haemophiliacs might be better served by introducing a vaccination policy (see later paragraph).

From this time on, the majority of studies and published investigations tended to relate to the more common severely affected patients with haemophilia A; however, the content can be extrapolated to patients suffering from haemophilia B. Mannucci et al 1975 found abnormal liver function tests and positive tests for hepatitis B in 40-60% of patients treated with a wide variety of products although he reported that most were free from clinical evidence of liver disease. In 1977 Biggs, writing in a letter to the British Journal of Haematology, reported that the incidence of jaundice in treated United Kingdom haemophiliac patients was 2.69%. The figure included patients with hepatitis B and the condition known as non-A non-B hepatitis.

The United Kingdom Haemophilia Centre Directors Hepatitis Working Party report of 1979 indicated that the prevalence of non-A non-B hepatitis for the year 1978-79 had been similar to that reported in 1976-77. However, there had been an increase in the proportion of non-A non-B hepatitis reported in patients with mild coagulation defects receiving concentrate for the first time. It was felt that the observed increase in these mildly affected patients was probably due to the fact that the more severely affected patients would have already been exposed to viruses present in all brands of concentrate and are therefore immune to re-infection. The same theme is continued in the Hepatitis Working Party's report for the year 1982-83.

I quote from a paragraph entitled: "Prospective studies of hepatitis in infrequently treated haemophiliacs":

"The study was commenced in Oxford in 1981 and the first six 30 patients, followed up after one transfusion of factor VIII concentrate for at least six months, are described. Of the 30 patients, four were excluded because they already had evidence of chronic liver disease. Two had received Cryoprecipitate and did not develop hepatitis. Of the remaining 24, 17 patients contracted non-A non-B hepatitis, nine after their first transfusion of factor VIII concentrate. Seven of these were after transfusion of one batch of NHS factor VIII, with a pool size of between 1,200 and 2,600 plasma donations.

This result confirms that the risk of contracting non-A non-B hepatitis is 100% on first exposure, whether the material is derived from the NHS or is commercial factor VIII concentrate. No cases of hepatitis B were observed, although 12 patients had evidence of past hepatitis B infection. It was determined that the incubation period for the non-A non-B hepatitis varied between one and 12 weeks."

The report confirmed that patients remained at risk from developing non-A non-B and from hepatitis B infection, the latter despite donor selection and the patients were being infected regardless of the source of their replacement treatment. Guidelines for hepatitis B vaccination were included in Appendix III of the same report. In 1982, only one vaccine for hepatitis B was licensed for use in the United Kingdom. In normal individuals, it was administered via the intramuscular route but the Centre Directors recommended that the same dose be administered subcutaneously for patients with bleeding disorder. Preliminary studies of the efficacy of vaccination were carried out in Oxford. There were variable results, with some patients developing only very weak immunity. The programme did not become readily established because, in 1983, worries were expressed that the source plasma of the vaccine could possibly have become contaminated by the putative AIDS-related virus. Indeed it was not for some years that utilising a recombinant-derived vaccine that hepatitis B vaccine became a routine.

During 1983-84, the full impact of the AIDS epidemic occurred. In order to prevent its transmission through blood products, virucidal techniques were introduced. Wet or dry heat treatment of concentrates was the initial method of choice. By this time the Northern Ireland Haemophilia Centre's factors VIII and IX were fractionated in Scotland (PFC). There the eventual heat treatment selected was dry heat at 80 degrees for 72 hours. This proved to be effective and eliminated both the HIV virus and the other lipid envelope viruses of hepatitis B and non-A non-B. Similar treatment was used in the English fractionation laboratories. On a worldwide basis, earlier selections of different temperatures and techniques were found to be ineffective. Despite early apprehension that the heat treatment of products might produce a

more immunogenic material, thankfully such fears remained unfounded. Factor IX concentrate was not heat treated until a later date through fears of producing a thrombogenic product. However, eventually it too became heat treated, with the addition of anticoagulant to prevent any thrombogenicity. As time went by, virucidal techniques improved and a solvent detergent technology replaced, in many instances, the original heat treatment. However, by the 1990s, virtually all new cases of HIV and hepatitis in treated haemophilic patients had been eliminated. However, there remained the problems of treating those who had already contracted viral infections.

It was estimated in the Northern Ireland Haemophilia Centre that 112 patients had been exposed to the possibility of virus infections following receipt of replacement treatment. 16 of those developed HIV infection, an incidence of just over 14%. The UK average infection rate was 44.5%. Seventy-six of the 112 developed hepatitis, an incidence of 72%. In some Centres in the United Kingdom, the incidence was as high as 95%. The rationale for these figures being slightly better than in other Centres in the United Kingdom was because it was a policy within the Centre that patients, as far as possible and practicable, should receive only product from one source. This was because it had become realised that using concentrate prepared from many different, large pools of plasma were likely to be more infective. The rationale was sound but the results were only partially effective.