Hepatitis C virus and transfusion transmitted liver disease: Review

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Introduction

Hepatitis has always been a well recognised complication of blood transfusion. Within the past year remarkable advances have been made in the characterisation of what seems to be the major causative agent of hepatitis associated with transfusions and the administration of clotting factors. There is now good evidence to implicate hepatitis C virus (HCV). Before summarising our current knowledge of HCV, the clinical and histological features of the condition formerly designated non-A, non-B hepatitis will be reviewed. It is now virtually certain, however, that in most cases of non-A non-B (NANB) hepatitis associated with transfusions or clotting factor concentrate this is synonymous with hepatitis C.¹ A few cases may be attributable to another as yet uncharacterised NANB virus, distinguishable from HCV by its chloroform insensitivity.² HCV may also be a common cause of sporadic hepatitis, but this review concentrates only on its association with blood transfusion and the administration of clotting factors.

The risk of hepatitis from injecting blood and preparations containing blood fractions, or from using needles contaminated with blood, led to the now abandoned term "serum" hepatitis. This contrasted with "infectious" hepatitis which usually occurred epidemically or sporadically with evidence of faecal-oral or at least non-parenteral transmission. Because the mode of transmission of these two immunologically distinct agents was not always so clearcut, hepatitis A and B were eventually substituted for the outmoded terms. Blumberg's seminal discovery of one of the antigenic markers associated with hepatitis B virus (originally called "Australia antigen" because it was first found in the serum of an Australian aborigine, but later designated HBsAg) allowed asymptomatic carriers who were potential blood donors to be identified. The risk of transmitting hepatitis B virus by blood transfusion was thus greatly reduced by blood donor screening. Hepatitis A virus is a lesser problem for several reasons: (i) the virus is directly cytopathic so it cannot be harboured without concomitant liver cell injury, thus a healthy carrier state is unlikely; (ii) the illness is usually mild and rarely becomes chronic; and (iii) the acute and possibly transmissible infection can be identified by testing the person's serum for the presence of an IgM antibody to the virus.

Recognition of non-A non-B hepatitis

Having screened out hepatitis B virus carriers, and bearing in mind that the hepatitis A virus is less likely to be transmitted in this way, many cases of liver disease occur following the

infusion of blood and blood products.^{3,4} The viruses responsible for this residual case population of post-transfusion hepatitis became known as the NANB viruses.⁴ They were called NANB viruses because the causative agents were elusive, their precise number was uncertain, and cases could be identified only by a process of elimination (A and B being serologically identifiable). There was good evidence from the variable incubation period and records of multiple infections in humans and chimpanzees that there were possibly several viruses in this category. Various studies have narrowed the cause of most cases of post-transfusion hepatitis down to probably just one of the NANB viruses; the culprit seems to be the NANB virus now designated HCV.

There remain, of course, other viruses in the NANB category such as those associated with enterically transmitted hepatitis and with a few cases of post-transfusion hepatitis. Enterically transmitted hepatitis has been described in outbreaks in India; the agent is water-borne, the hepatitis is often associated with more cholestasis than is seen in post-transfusion non-A non-B hepatitis, and there is much less risk of chronicity.⁵ Their name is, as yet, undecided. "hepatitis D virus" is a label which has been used for delta agent, a defective virus requiring HBV for pathogenicity, and might therefore be ambiguous if applied to any other subsequently discovered hepatitis virus.

Natural history of hepatitis associated with transfusion and clotting factor administration

The infection is characterised by an incubation period of about 60 days, a clinically mild and often asymptomatic illness, but often with progression to chronic hepatitis and consequently cirrhosis.⁶⁻¹⁰ Serum transaminase activities characteristically fluctuate. It has been estimated that chronic hepatitis ensues in about half of all infected cases.¹

NANB hepatitis has become a serious problem in haemophilic patients and in those with Christmas disease. Its importance has been obfuscated by the prominence given to the undeniably serious problem of AIDS in haemophilic patients, but the prospect of managing bleeding oesophageal varices in a patient with congenital factor VIII deficiency and the acquired clotting factor deficiencies due to liver failure should be enough to demand attention.¹¹ The precise interaction between HIV and hepatitis viruses awaits clarification.

Chronic liver diseases in haemophilia

Following the introduction of clotting factor

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concentrates prepared from large (more than 2000) donor pools in the 1970s it was realised that there was an increased incidence of liver disease evinced by episodes of clinically overt hepatitis or biochemical abnormalities such as raised serum transaminase activities.^{12,13} Particularly worrying was the observation that the abnormalities of liver biochemistry persisted for six months or more and showed no signs of abating. In the absence of clotting factor abnormalities most patients with this pattern of liver biochemistry would have had a percutaneous liver biopsy performed; there was, understandably, some reluctance to do this in patients with haemophilia. A few groups of investigators, however, have undertaken a study of chronic liver disease in haemophilic patients, taking biopsy specimens under clotting factor cover and with few complications.¹⁴

These biopsy studies have shown that there is a high incidence of chronic liver disease in haemophilic patients who received clotting factor concentrates.^{14,15} Almost all patients have some form of chronic hepatitis ranging from chronic persistent hepatitis in most to chronic active (aggressive) hepatitis; a few have evidence of cirrhosis on their initial biopsy specimen. Chronic active hepatitis pursues a fairly typical course in these patients and frequently progresses to cirrhosis, which is confirmed by repeat biopsies or at necropsy. Particularly disturbing, however, is the observation that chronic persistent hepatitis, usually regarded as a benign self limiting pattern of chronic inflammation, is associated with a high risk of progression to chronic active hepatitis and cirrhosis.¹⁴ This feature of chronic hepatitis in haemophilic patients is probably attributable to the nature of the causative agent rather than to the fact that the patients are being repeatedly exposed to infecting doses in the clotting factor concentrates. Not all investigators are convinced of the progressive course of chronic liver disease in these patients, however,⁷ and some claim that the incidence of chronic active hepatitis is no greater in concentrate users than it is in those haemophilic patients treated with cryoprecipitate.¹⁸

Histology of non-A, non-B hepatitis

Liver histology in hepatitis associated with transfusions or clotting factor concentrates shows several fairly consistent features which are unusual in hepatitis due to viruses A or B or to other aetiologies of inflammatory liver disease such as alcohol and drugs.¹⁹⁻²⁴ These features include:

- 1 Focally dense infiltrates of lymphocytes in portal tracts. The infiltrates are often tightly aggregated, like follicles, and sometimes contain germinal centres.
- 2 Fatty change (steatosis) which may be panacinar and is often microvesicular.
- 3 Intravascular sinusoidal infiltrates of lymphocytes or Kupffer cell hyperplasia, or both, in the absence of a concomitant degree of liver cell necrosis in the immediate vicinity.
- 4 Abnormal bile duct epithelium mimicking that seen in the early lesions of primary biliary hepatitis. This feature is seen least commonly

but is reported to be the most important histological marker for predicting chronicity.

These features are, of course, often superimposed on those common to other types of viral hepatitis, except that cholestasis is uncommon. There are varying degrees of architectural disturbance as the disease progresses and, in assessing these biopsy specimens, it is important to record both the type of chronic hepatitis (CPH or CAH) and whether these aetiological markers are present. The characteristic histological features probably wane as the disease progresses. Some features, such as the sinusoidal infiltrates, simulate the hepatitis associated with cytomegalovirus and the Epstein-Barr virus.

Characterisation of hepatitis C virus

The virus responsible for most cases of NANB hepatitis associated with transfusions or clotting factor concentrates has now been identified and characterised.^{25,26} It has been designated "hepatitis C virus". Hepatitis C virus is a lipid enveloped, single stranded RNA virus of the togavirus or flavivirus category (the yellow fever virus is a member of the latter group).²⁷ Investigators at the Chiron Corporation in the United States of America have synthesised an antigen (C100-3) which is now being used to screen for the hepatitis C virus antibody by radioimmunoassay²⁵ or enzyme immunoassay in clinical cases and, in the near future in the United Kingdom, in prospective blood donors. Anti-HCV antibodies have been found in a high proportion of patients with NANB hepatitis following blood transfusions or the administration of clotting factor concentrates; it seems to be a reliable marker.^{1,28,29}

It is not yet known whether HCV is directly cytopathic, like HAV, or damages the liver through the immune deletion of infected liver cells bearing virus associated antigens, like HBV. From observations on biopsy specimens from NANB hepatitis, however, the widespread acidophilic change seen in hepatocytes in acute cases and the relative lack of lymphocytes in the immediate vicinity suggests that HCV is cytopathic.²¹

Interferon treatment for hepatitis C

At the same time as the HCV virus was being characterised, clinical trials of interferon α for NANB hepatitis were being undertaken.³⁰⁻³² Interferon α has a wide spectrum of antiviral activity and is known to inhibit the replication of HAV, HBV, and delta agent. It is logical, therefore, to consider it for treating HCV hepatitis, particularly in view of the absence of any other suitable treatment and the high risk of progression to cirrhosis. Recently published studies show that interferon α does inhibit disease activity in HCV hepatitis as judged by normalisation of serum transaminase activities and a reduction in the degree of inflammation seen in liver biopsy specimens.³¹ The treatment is, however, not curative and many patients relapse when interferon is withdrawn. Nevertheless, this form of treatment may be worth pursuing in view of the high risk of progression

of HCV hepatitis to cirrhosis, a condition with morbid and mortal consequences at least as great as those associated with many forms of cancer.

Hepatitis C and hepatocellular carcinoma

It is suspected that HCV may have an important role in the development of some cases of hepatocellular carcinoma.³³⁻³⁵ In Japan there is reported to be an increasing incidence of hepatocellular carcinoma that is not associated with hepatitis B virus; up to 30% of cases of HBV negative hepatocellular carcinoma have a history of blood transfusion.³⁶ Surveys of stored serum samples from patients with hepatocellular carcinoma have shown a high incidence of anti-HCV antibodies.³⁷⁻³⁹ The incidence is high (40% in one study) even in patients without cirrhosis, so the association may not require the presence of this precursor condition and may, therefore, more directly implicate HCV in the pathogenesis of the neoplasm.

Conclusions

HCV has now been fully characterised. It is responsible for most cases of hepatitis associated with transfusions or the administration of clotting factors. The hepatitis, formerly designated post-transfusion NANB hepatitis, is histologically distinguishable in many cases by fatty change, follicular lymphocytic infiltrates in portal tracts, and sinusoidal infiltration. HCV hepatitis is often chronic and progresses to cirrhosis, but can be improved, though not cured, by treatment with interferon α . Anti-HCV antibodies have been found in a significant proportion of cases of hepatocellular carcinoma and there is, therefore, a suspicion that the virus may be oncogenic.

Genetically engineered clotting factors will, of course, be free from the risk of transmitting HCV, HIV, and other viruses, but many survivors of the era of clotting factor concentrates will have to live out the legacy of chronic liver disease. Similarly, exclusion, by antibody testing, of HCV positive blood donors should reduce very substantially the risk of transmitting this virus to transfusion recipients, but many patients have already been infected and the consequences will still be evident in the next century. Furthermore, the administration of blood and clotting factors is only one of several modes of transmission of hepatitis C virus⁴⁰; screening and prophylaxis will be less easy to implement in other situations. This is yet another iatrogenic disease from which we have much to learn.

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