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Unresolved issues in non-A, non-B hepatitis

by

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The specific diagnosis of hepatitis types A, B and D revealed a previously unrecognised form of hepatitis which is clearly unrelated to any of these three types. Results obtained from several surveys of post-transfusion hepatitis in the USA and elsewhere provided strong epidemiological evidence of "guilt by association" of an infection of the liver referred to as non-A, non-B hepatitis. This is now the most common form of hepatitis occurring after blood transfusion in some areas of the world. More direct evidence of at least two transmissible agents in non-A, non-B hepatitis has come from experimental transmission to chimpanzees and cross-challenge with known infectious inoculation after recovery. Studies have also shown that this infection occurs in haemodialysis and other specialised units, that it occurs in a sporadic form in the general population, that it can be transmitted by therapeutic plasma components and that a prolonged carrier state in the blood may occur. There is also considerable evidence that the parenterally-transmitted infection, like hepatitis type B, may progress to chronic liver disease in about 50% of patients, and preliminary information of an association with hepatocellular carcinoma.

Epidemiology

Parentally transmitted non-A, non-B hepatitis has been found in every country in which it has been sought and shares a number of features with hepatitis B. This form of hepatitis has been most commonly recognised as a complication of blood transfusion, and in countries where all blood donations are screened for hepatitis B surface antigen by very sensitive

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techniques non-A, non-B hepatitis may account for as many as 90% of all cases of post-transfusion hepatitis. Outbreaks of non-A, non-B hepatitis have also been reported after the administration of blood-clotting factors VIII and IX. Non-A, non-B hepatitis has occurred in haemodialysis and other specialised units, among drug addicts and after accidental inoculation with contaminated needles and other sharp objects and occasionally maternal to infant transmission has been reported.

Although in general the illness is mild and often subclinical or anicteric, severe hepatitis with jaundice does occur and the infection is a significant cause of fulminant hepatitis. There is considerable evidence that the infection may be followed in many patients, and in experimentally infected chimpanzees, by prolonged viraemia and the development of a persistent carrier state. Studies of the histopathological sequelae of acute non-A, non-B hepatitis infection revealed that chronic liver damage, which may be severe, may occur in as many as 40-50% of the patients.

Clinical, epidemiological and experimental studies in several laboratories indicate that non-A, non-B hepatitis may be caused by two and possibly more than two infectious agents. Clinical evidence is based on the observation of multiple attacks of hepatitis in individual patients. Epidemiologically, short-incubation (2-5 weeks) and long-incubation (5-10 weeks or longer) forms of non-A, non-B hepatitis have been described. The incubation period, however, does not appear to be a reliable index for differentiating between the two non-A, non-B types of hepatitis, and it is likely that differences in the incubation period represent differences in the infective dose. Experimental evidence for the existence of at least

two distinct non-A, non-B hepatitis viruses has been obtained from cross-challenge experimental transmission studies in chimpanzees in at least four independent laboratories, but final confirmation must await the availability of specific laboratory tests and the identification and characterisation of the virus(es).

The viruses

The virus(es) causing the parenterally-transmitted form of non-A non-B hepatitis have not been identified (although numerous particles have been described), and their mode of replication and antigenic composition remain unknown despite intensive efforts in many laboratories throughout the world. There is no homology between hepatitis B virus, the delta hepatitis virus and the non-A, non-B agents.

Various types of virus particles have been described in the serum, urine, some implicated blood products, hepatocytes and kupffer cells, but independent confirmation has not been obtained. It appears that an RNA virus has been cloned successfully by recombinant DNA techniques in a laboratory in the USA and independently in another laboratory in Japan, and specific antibody has been detected in convalescent sera of a well-documented panel of non-A, non-B specimens, as well as in a proportion of blood donors in the USA and in Japan. Scientific data are not yet published, but the availability of specific laboratory tests for the parenterally-transmitted forms of non-A, non-B hepatitis will be a significant development.

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Virus-like particles (60-70nm) with an envelope with surface projection budding into cell vacuoles and rod-shaped inclusions were detected in nuclei of hepatocytes from a British patient transplanted for sporadic non-A, non-B fulminant hepatitis, probably contracted in Kenya. Identical particles were seen in two successive liver grafts (days 2 and 10) at regrafting for recurrent FHF. Ultrastructural features resembled those of the RNA-containing arbovirus, Rift Valley Fever Virus, but serological studies of arboviruses (Togaviruses) and transmission in mice proved negative. The particles shared features with the different arboviruses seen in the hepatectomy specimen of another patient with fulminent non-A, non-B hepatitis in whom an insect vector was implicated and were identical in size to those in a third patient with fulminant non-A, non-B hepatitis, who had remained in [illegible] Kingdom. These findings, together with the recent unpublished report of isolation of an RNA-containing virus resembling the Togaviridae, in parenteral non-A, non-B hepatitis, suggest that viruses resembling the arboviruses, but not transmitted by an insect vector, may be involved in the aetiology of non-A, non-B hepatitis, including in the sporadic forms of fulminant hepatitis in the United Kingdom (Fagan E A, Ellis D S, Tovey G, Lloyd G, Portmann B, Zuckerman A J and Williams R, in press).

Surrogate tests

Until specific tests become widely available for non-A, non-B hepatitis several "non-specific" (surrogate) tests have been recommended for screening units of blood.

Two large studies were conducted to assess the role of anti-HBs detected in blood donor units in the subsequent development of non-A, non-B

hepatitis. Although the studies did show a higher incidence of hepatitis in recipients of anti-HBs -positive blood, subsequent reports indicated that it was not related to the presence of anti-HBs per se, but to the higher frequence of anti-HBs in commercial blood. Others, however, failed to confirm the association between anti-HBs in donor blood and the increased risk of non-A, non-B hepatitis in recipients.

The Transfusion-Transmitted Viruses (TTV) Study Group proposed that units of blood which were positive for anti-HBc were associated with a 2-3 fold greater risk of non-A, non-B hepatitis in recipients than were units without anti-HBc. This was confirmed more recently by a study which suggested that by excluding anti-HBc-positive donors, 54% of non-A, non-B cases may be prevented, with a donor loss of only 4%.

However, the non-specific indicator which has received most attention is serum aminotransferase levels in blood donors. Several studies have shown that the risk of non-A, non-B post-transfusion hepatitis is directly related to the serum alanine aminotransferase (ALT) level of the donor. However, it was concluded that exclusion of blood units with serum ALT levels of 53 IU/litre or more would prevent 29% of post-transfusion hepatitis with a loss of only 1.6% of donor units. This method is thus better than screening for anti-HBc since the corrected efficacy of anti-HBc as a screening test was slightly less than that of ALT and the number of blood units lost would be twice those which would be if ALT were used. But the sensitivity of the test for ALT is only 26%, and despite the high specificity, the predictive value is only 42%. Thus almost two

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out of three units of blood with an elevated ALT level will not transmit non-A, non-B hepatitis. ALT levels vary with age, sex, alcohol use and geographical region and would therefore not be useful as a surrogate marker of non-A, non-B hepatitis.