Regular Review

Non-A, non-B hepatitis: Dead ends or new horizons?

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Researchers who work on hepatitis may sometimes think that they have come to a dead end with non-A, non-B hepatitis, but in recent years there has been gradual progress in knowledge about these diseases. A hepatitis A like agent that causes epidemic waterborne non-A, non-B hepatitis has been characterised, and the epidemiology of the different forms of non-A, non-B hepatitis has been clarified.

The diagnosis of non-A, non-B hepatitis, which may be a problem in routine clinical work, is usually based in scientific reports on serum alanine transferase activity being raised to at least twice the upper normal limit on at least two occasions one or more weeks apart. Other causes of raised serum alanine transferase activity, such as drug reactions and infections with cytomegalovirus and Epstein-Barr virus, have also to be excluded.

TABLE I—Reported incidence of non-A, non-B hepatitis among patients with hepatitis in different parts of the world

Place (and reference)	Study period (years)	No of patients studied	% with non-A, non-B hepatitis
Gothenburg, Sweden (Norkrans <i>et al</i> ³¹)	5	480	14
Heidelberg, West Germany (Ehrlich <i>et al</i> ³⁸)	5	434	15
Milan, Italy (Careda <i>et al</i> ¹²)	1.5	314	22
Baltimore, USA (Alter <i>et al</i> ¹⁰)	1.5	253	24
Melbourne, Australia (Lucas <i>et al</i> ³⁹)	1	1006	21
Tokyo, Japan (Furuta <i>et al</i> ⁴⁰)	1	102	47

World wide, non-A, non-B hepatitis seems to represent 15-25% of clinical cases of viral hepatitis, although it seems more common in Japan (table I). Three epidemiological types of non-A, non-B hepatitis have been recognised: the waterborne epidemic type; the blood or needle associated type; and the sporadically occurring (community acquired) type.

Epidemic non-A, non-B hepatitis

Non-A, non-B hepatitis was distinguished from hepatitis A and hepatitis B in the 1970s.^{1,4} More recent epidemiological data as well as an experimental study have confirmed the existence of a hepatitis A like form of non-A, non-B hepatitis,⁵⁻⁹ often called epidemic non-A hepatitis. The prevalence of this type, which is transmitted by the faecal-oral route, is not known. The viral aetiology was confirmed

by a volunteer being infected through ingesting faecal material obtained from patients in Moscow with non-A, non-B hepatitis.⁹

This type of non-A, non-B hepatitis has been seen in epidemics in developing countries in Africa and Asia. Its epidemiology resembles that of hepatitis A, but the virus is serologically unrelated to hepatitis A virus and can infect patients who have recovered from hepatitis A.

Epidemic non-A, non-B hepatitis is usually transmitted by water supplies contaminated by faeces infected with the virus. Secondary cases among household contacts suggest that person to person spread may also occur. There may also be an association with consumption of shellfish in the United States of America and Europe.¹⁰⁻¹²

Epidemic waterborne non-A, non-B hepatitis resembles hepatitis A not only epidemiologically but also clinically. About half of the patients have a fever, but otherwise symptoms are mild. The slightly or moderately raised serum alanine transferase activity usually resolves within six to eight weeks, and the disease has never been known to become chronic. Epidemic waterborne non-A, non-B hepatitis may, however, present as fulminant hepatitis, and mortality in these rare cases may be 10%, or even higher in pregnant women.^{13 14}

Parenterally spread non-A, non-B hepatitis

Non-A, non-B hepatitis appears to be transmitted most often percutaneously. This type is seen in recipients of blood or blood products and in drug addicts. The incidence of non-A, non-B hepatitis in recipients of blood from volunteer donors in the United States ranges from 4% to 12% with an average of 7%.¹⁵ Today over 90% of cases of hepatitis after transfusion in the United States and elsewhere are of non-A, non-B hepatitis.

The structure and size of this bloodborne virus are unknown. There have been several reports of virus like particles of different sizes, but no particle has been consistently identified. The virus is inactivated by formalin and chloroform and by heating at 60°C for 10 hours. It can be transmitted to chimpanzees, which develop characteristic convoluted tubules in their hepatocytes.

Recently retrovirus like particles were described in the hepatocytes of patients with non-A, non-B hepatitis transmitted by blood.¹⁶ The same group also claimed finding reverse transcriptase in the serum of these patients.¹⁷ The

findings fit well with the chronic course of non-A, non-B hepatitis transmitted by blood, and this initial report was met with enthusiasm. Other researchers, however, had great difficulty confirming these findings,¹⁸ and only recently has an Italian group reported similar findings to those of the Bethesda workers and supported the retrovirus hypothesis.¹⁹ More evidence is needed to confirm the hypothesis that a retrovirus may cause bloodborne non-A, non-B hepatitis, but the hypothesis could explain many oddities about the agent(s) that cause parenterally spread non-A, non-B hepatitis.

Patients with acute non-A, non-B hepatitis transmitted by blood may present with fever, but symptoms are usually mild and three quarters of patients have no jaundice. Many patients, however, develop chronic disease. Non-A, non-B hepatitis may also be transmitted by antihæmophilic factor and by factor IX complex. In fact most hæmophiliacs receiving commercial clotting factor concentrates made from large plasma pools develop non-A, non-B hepatitis.

Lever *et al* in 1984 reported non-A, non-B hepatitis in 12 immunodeficient patients who had been treated with an intravenous immunoglobulin.²⁰ A similar outbreak occurred in other immunodeficient patients after the introduction of a new intravenous preparation of immunoglobulin.²¹ One year or more after the acute infection at least half of the patients reported on by Lever *et al* had progressive liver disease. Similar experiences have been reported from Sweden.^{22, 23} It is not known why certain intravenous preparations of immunoglobulin transmit non-A, non-B hepatitis, but the absence of non-A, non-B hepatitis in recipients of intramuscular immunoglobulin that may come from the same original pool of plasma suggests that variations in the manufacturing process allow the non-A, non-B agent(s) to remain infectious in the intravenous preparation.

Transmission studies and cross challenge experiments in chimpanzees have suggested a second bloodborne non-A, non-B hepatitis agent that is preferentially transmitted by commercial coagulation factor concentrates.²⁴

The occurrence of second episodes of non-A, non-B hepatitis in man^{1, 25, 26} and in experimentally infected chimpanzees is further evidence for a second agent associated with blood. This second agent may cause non-A, non-B hepatitis in hæmophiliacs, who are supposed to be immune to the non-A, non-B hepatitis virus usually transmitted by blood.^{27, 28} It is, however, not known if there is any real immunity after non-A, non-B hepatitis that follows transfusion. Some data show that chimpanzees can be reinfected with the same inoculum of non-A, non-B hepatitis if the dose is increased 100-fold.²⁹ This observation may speak against the hypothesis of two bloodborne agents.

Some evidence has been presented that a fraction of cases of bloodborne non-A, non-B hepatitis may be caused by a variant of hepatitis B virus. Monoclonal antibodies and hepatitis B virus DNA probes have been used to detect specific antigenic determinants and partially homologous nucleic acid in the serum and liver of patients and infected chimpanzees.³⁰ Critics of this report have asked for controlled studies to show the specificity of both methods. A prospective controlled study should be done to establish the value of these tests, if any, in preventing post-transfusion non-A, non-B hepatitis.

Drug addicts who inject are well known victims of non-A, non-B hepatitis, and in many series of non-A, non-B hepatitis drug addicts represent most of the cases.^{10, 31, 32} In a recent report from Italy that included 151 drug addicts with viral

hepatitis about a quarter had non-A, non-B hepatitis.³³ As infection with the blood transmitted non-A, non-B hepatitis agent(s) is often chronic, drug addicts may represent an important reservoir of non-A, non-B hepatitis.

Sporadically occurring (community acquired) non-A, non-B hepatitis

Cases of non-A, non-B hepatitis that seem to be unconnected with blood, blood products, or drug addiction are often referred to as "sporadic" or "community acquired." In some series this type constitutes about a quarter of the cases of non-A, non-B hepatitis. Unapparent parenteral transmission by blood or through sexual contacts may be possible mechanisms of virus transmission in these cases, but sporadically occurring cases of the epidemic type of non-A, non-B hepatitis may also occur.

Caredda *et al* recently described 20 patients with non-A, non-B hepatitis associated with shellfish¹² who showed the same clinical characteristics as cases in a waterborne outbreak of non-A, non-B hepatitis,⁵ and Alter *et al* found an association between shellfish and non-A, non-B hepatitis in Baltimore.¹⁰ Such cases may well represent non-epidemic spread of the epidemic waterborne type of non-A, non-B hepatitis: the short incubation period (average three weeks) seemed to be similar and so was the rarity of chronic infection.

Chronic infection with the non-A, non-B hepatitis agent(s)

After being exposed to the parenterally transmitted non-A, non-B hepatitis agent(s) most individuals are likely to become carriers. The fact that blood donors commonly transmit non-A, non-B hepatitis to recipients strongly suggests that there is an asymptomatic carrier state. Experimental transmission of non-A, non-B hepatitis from asymptomatic individuals to volunteers as well as to chimpanzees has proved this. In one study serum from a single donor collected over six years remained persistently infectious.²⁴ The carrier state must be common as post-transfusion non-A, non-B hepatitis occurs in several per cent of American recipients of a single unit of blood.¹⁵

The usual pattern in chronic forms of non-A, non-B hepatitis is irregular rises in serum aminotransferase activity. Periods of normal or near normal activity alternate with periods of raised enzyme activity that may last months or years. Clinical symptoms may or may not parallel these biochemical changes. Several studies have shown that chronic liver disease is very common after non-A, non-B hepatitis transmitted by transfusion: up to two thirds of patients have raised serum alanine transferase activity six months after the onset of infection (table II).

In cases with no history of transfusion the incidence of chronic disease is more variable. Studies in Scandinavia have shown that under 15% of patients with sporadically occurring non-A, non-B hepatitis have raised serum alanine transferase activity at six months.^{31, 32} In British and American reports chronic infection was observed in more than 40% of such cases, but these studies included drug addicts, in whom chronic non-A, non-B hepatitis is known to be common.¹⁰ Chronic hepatitis is also common in those infected by clotting factors (table II), and raised aminotransferase activity has been reported in up to 100% of hæmophiliacs.³⁴

TABLE II—Chronicity of non-A, non-B hepatitis as determined by raised serum aminotransferase activity (ALT) six months after onset of illness in different epidemiological types of non-A, non-B hepatitis

Epidemiological type	Investigators	No of patients studied	% Of patients with raised ALT at 6 months
Transmitted by blood transfusion	{ Alter <i>et al</i> ⁴¹ Realdi <i>et al</i> ⁴²	55 21	55 67
Transmitted by coagulation factors	{ Bamber <i>et al</i> ³⁴ Rickard <i>et al</i> ⁴³	10 66	100 44
Community acquired (sporadic)	{ Norkrans <i>et al</i> ³¹ Müller <i>et al</i> ⁴⁴	56 40	7 13
Epidemic, waterborne	Khuroo <i>et al</i> ⁵	30	0

Treatment and immunoprophylaxis

There is no effective treatment for non-A, non-B hepatitis. Corticosteroids are not beneficial, but long term low dose treatment with recombinant α interferon in chronic non-A,

non-B hepatitis was partly successful in controlling the disease activity.³⁵ This enthusiastic preliminary report has yet to survive a properly controlled study.

Some studies have suggested that certain lots of immunoglobulin can reduce icteric cases of non-A, non-B hepatitis after transfusion,^{36,37} but efficacy cannot be properly evaluated until the disease can be diagnosed serologically and until the antibody in the immunoglobulin preparation can be measured.

The prospects for developing a vaccine against one or more of the agents of non-A, non-B hepatitis are hard to evaluate. A vaccine against the bloodborne agent(s) would be welcome but still seems far away.

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