Review Article

Transfusion transmitted viral infections – recent developments in blood donor screening

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Introduction

Transmission of infectious diseases by the administration of blood, its components or derivatives, has been known since the beginning of transfusion. However, 50 years ago, syphilis was the only disease which was serologically screened. Post-transfusion hepatitis (PTH) occurred in about 30% of blood recipients in the US, but no laboratory test was available before 1969. During the last 20 years, the striking increase in the use of blood components and derivatives, and advances in the knowledge of diseases transmitted by blood has made this an area of major technological change, particularly where the screening of blood donors is concerned (Table I). In addition, the fear of developing the acquired immunodeficiency syndrome (AIDS) after transfusion has resulted in transfusion transmitted disease becoming a matter of major public concern, with significant effects on transfusion practice, and the acceptability to the individual patient of treatment with blood and blood products. The medico-legal consequences of blood transfusion have been highlighted by patients who have contracted human immunodeficiency virus (HIV) infection suing physicians, hospitals and transfusion centres and even demanding to know the identity of the blood donor who was the source of the infection. This brief article will concentrate on recent findings concerning the serological screening of blood donations in relation to transfusion transmitted viral infections in the last few years.

The safety of blood and blood products with respect to transfusion transmitted infections depends primarily on the detection of the asymptomatic carrier with clinically unapparent disease. In addition, other factors may play an important role in the transmission of viral infections. Such factors include the amount of the infectious agent in the blood, the type and amount of blood or blood component transfused, the viability of the infec-

Table I   Transfusion transmitted viral infections

Virus	Status of Screening Test
Hepatitis B	Routinely tested in all donations
HIV-1	Routinely tested in all donations
HIV-2	Routinely tested in all donations in UK and a few other countries
Hepatitis C	To be introduced in the near future
Cytomegalovirus	Screening occurs for a proportion of blood donations
Delta virus	Excluded by screening for HBsAg
Non A, non B virus	Screening undertaken in USA by testing for surrogate markers (ALT, Anti-HBc). No plans to introduce this routinely in the UK
HTLV-1	Screening possible but problems exist with cross reactivity with other retroviruses including HTLV-2
EBV	No plans for screening to be introduced
Parvovirus B19	No plans for screening to be introduced

HIV = human immunodeficiency virus; HTLV = human T cell leukaemia/lymphoma virus; EBV = Epstein Barr virus; ALT = alanine aminotransferase. HBsAg = hepatitis B surface antigen; HBc = hepatitis B core antigen.

tious agent on storage of the blood and the susceptibility of the recipient to the virus infection.

Viral hepatitis

Viral hepatitis has long been recognized as the most common infection transmitted by donor blood and it is a cause of serious short term and long term morbidity. Hepatitis A is a rare cause of viral hepatitis as it only has a very brief period of viraemia and a subsequent carrier state does not exist. However, by contrast, prior to its

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identification, hepatitis B was considered the most frequent and serious form of PTH. Although hepatitis B (HBV) is a highly infective virus, the introduction of routine donor screening for hepatitis B surface antigen (HBsAg) reduced cases of PTH in the US by about a third. Furthermore, the active immunization of certain blood product recipients such as haemophiliacs with hepatitis B vaccine, has markedly reduced the incidence of transfusion transmitted hepatitis B infection. The very few cases that still do occur are usually related to blood donors in whom the concentration of circulating HBsAg is below the level of detection in routine screening assays. However, newer HBsAg assays are highly sensitive and such incidents are fortunately extremely rare.

The majority of cases of PTH today are designated as due to non A, non B hepatitis (NANBH). The exact incidence of NANBH in the UK is not known but pilot studies in the UK suggest that it is of the order of 1% (J. Barbara, personal communication). The major recent discovery in relation to NANBH has been in the identification of a new virus which has been designated hepatitis C virus (HCV).[1] A serological test is available to detect individuals infected with HCV based on the detection of HCV antibody.[2] However, it has been suggested that all such individuals, although HCV antibody positive, are potentially infectious, in a manner analogous with HIV antibody-positive individuals.

Initial studies have suggested that up to 80% of cases of transfusion-associated NANBH are anti-HCV positive and it is hoped that HCV antibody screening of blood donors will be routinely introduced in the second half of 1990 in the UK. However, there remain a number of, as yet, unresolved problems that may influence the effectiveness of such measures. The HCV antibody test developed for routine screening does not identify all individuals infected with HCV. In particular, there may be a long window period of up to a year after primary infection when antibodies to HCV are undetectable in the conventional serological test. In addition, there is at present no generally accepted confirmatory test for HCV infection, thus the extent of false-negative and false-positive reactions obtained on screening is not yet known. The precise degree of infectivity of HCV antibody positive blood is not yet known but by analogy with HBV, it is possible that infected individuals may differ in whether they are active carriers of the virus or not. Indeed, it is possible that the majority of anti-HCV positive donor samples identified in the current test are non-infectious. Finally, it is unclear whether asymptomatic blood donors who have been found to be anti-HCV positive should be investigated further, and what advice about their prognosis

should be given.

One point of concern about the introduction of HCV screening is whether such a measure will make unnecessary the introduction of alanine aminotransferase (ALT) screening of blood donors in the UK, or replace it in the USA. ALT is an enzyme synthesized in the liver and levels are raised in a number of different conditions including viral hepatitis and other forms of liver disease, obesity, exercise, alcohol ingestion and after administration of a wide variety of drugs. The introduction of this test in the USA was because two studies[3,4] had indicated that the incidence of post-transfusion hepatitis was related to the ALT levels in the blood donor. Although donors with ALT levels in the normal range were still capable of transmitting NANBH, the incidence of PTH in transfusion recipients increased in proportion to the donor ALT level. Thus routine screening of this 'surrogate' marker to exclude donors with raised ALT levels was initiated in the USA in 1986. Similarly, antibody to hepatitis B core antigen (anti-HBc) was proposed as a 'surrogate' marker for NANBH, and screening of donors for this additional marker was therefore introduced in 1987. However, to date, no conclusive evidence of the effectiveness of either procedure in preventing PTH has been provided. The role of ALT and anti-HBc screening in the prevention of PTH therefore remains unclear and may remain so after the routine introduction of HCV antibody screening.

Another cause of viral hepatitis is hepatitis D virus or delta agent. This virus is an incomplete RNA virus that cannot survive on its own, but requires the helper function of a DNA virus, usually hepatitis B, for replication; it exists as a core of delta agent antigen, surrounded by a capsule of HBsAg. Delta hepatitis occurs as a result of simultaneous infection with both HBV and the delta agent or with transmission of the delta agent to a person who is either a carrier for, or chronically infected with, HBV. However, the screening of all donors for HBsAg will also screen carriers of the delta agent indirectly.

Retroviral infections

In 1985, a serological method for the screening of blood donors for HIV was introduced, after evidence was published a year before of a series of cases of AIDS, where transfusion was the only risk factor. As a result, the incidence of HIV transmission by blood has now virtually ceased. However, a number of concerns have been raised regarding the value of HIV antibody screening. Firstly, there exists a 'window' between HIV primary infection, during which the individual is infectious, and seroconversion. Extremely rare cases of transmission due to blood transfusion during this window

period have been reported.[5] However, the risk of such transmission is extremely low, and is probably of the order of 1:100,000, or less, in the UK. Secondly, an unquantifiable but important component of screening procedures to eliminate transfusion transmitted HIV infection has been the use of blood donor exclusion criteria. These criteria attempt to exclude high-risk groups for AIDS such as homosexual or bisexual men, intravenous drug abusers, prostitutes, haemophiliacs and sexual partners of high-risk individuals. Such criteria become less reliable in communities where heterosexual transmitted HIV infection is occurring, as individuals may have no prior knowledge of the likelihood of their sexual partner being at risk for HIV infection. Thirdly, there have been a small number of reports of individuals, belonging to high risk groups who appear infected with HIV but remain persistently seronegative.[6,7] Such reports are controversial at present and it is not known whether such asymptomatic donors could transmit HIV through blood. In addition, where the polymerase chain reaction is used for the detection of HIV, contamination resulting in false positive results has been observed. Thus the status of such reports remains unclear at the present time. Finally, most of the routine screening tests in use are for HIV-1 but screening for HIV-2 has recently been introduced in some countries, including the UK. Although there are very few cases of HIV-2 in the UK, and testing would not appear to be cost-effective, theoretical concerns and the availability of a screening test appear to have produced pressure for an extension of HIV testing.

Another retrovirus is human T cell leukaemia virus-1 (HTLV-1) which was the first human retrovirus to be identified. Clinically it is associated with a specific T-cell malignancy, adult T-cell leukaemia or lymphoma, and epidemiological studies have shown a relationship between an increased frequency of antibodies to HTLV-1 and areas where there have been clusters of this otherwise uncommon T-cell malignancy. The infection is endemic in the Caribbean, parts of Africa and Japan and individuals who are HTLV-1 antibody positive may transmit the disease by transfusion of cellular components of blood. Once infected, the lifetime risk of developing adult T-cell leukaemia is of the order of 2–5%. Screening tests are available to identify infected blood donors, but confirmation of positive results is difficult due to cross reaction with other viruses. In particular, differentiation between HTLV-1 and HTLV-2 is difficult and some of the previous reports about infection with HTLV-1 in intravenous drug abusers may have been due to HTLV-2. Due to these uncertainties, and the priority for introducing HCV screening, no date has yet been set for introducing HTLV-1 screening in the UK.

Cytomegalovirus infections

Post-transfusion cytomegalovirus (CMV) infection may occur as a primary infection in a previously unexposed person or may involve reactivation of infection or even reinfection with a different strain of CMV. In immunocompetent individuals, transfusion-associated CMV is a mild or inapparent infection. However, in certain immunocompromised patients, such as low birth weight babies, and CMV-negative recipients of bone marrow or cardiac transplants, CMV may cause a very serious, often fatal, multisystem disease which includes pneumonitis, hepatitis and gastroenteritis. CMV is transmitted by all leucocyte-containing blood products, including whole blood, red cell concentrates, platelet and granulocyte concentrates, and blood from CMV antibody-negative donors is very uncommonly associated with CMV transmission. Thus CMV-negative blood should be used for transfusion in the above patient groups. If CMV-negative blood is not available, leucocyte-rich preparations, such as granulocyte transfusions should be avoided, if possible, and leucocyte filtration of other cellular products considered, although the efficacy of this procedure is unproven.

Other viruses

Two other viruses that are transmitted by blood are Epstein-Barr virus (EBV) and parvovirus B19. EBV causes lifelong infection, with approximately 90% of adults showing evidence of prior infection but is rarely transmitted by transfusion. This may be because the majority of adult transfusion recipients are already immune and even those who are not may receive passive transfer of EBV antibody with transfusion of plasma-containing products. Reduced viability of B lymphocytes infected with EBV in stored blood may also be a factor in reducing transmission. Nonetheless, EBV has been associated with post-transfusion mononucleosis, although the majority of such cases are probably due to CMV. Other cases of transfusion-associated EBV have occurred in immunocompromised patients but due to the mildness of EBV-related disease, there are no plans to introduce screening.

The recently identified parvovirus B19 is of more interest since it can cause aplastic crises in patients with sickle cell disease or chronic haemolytic anaemia. However, in general, parvovirus B19 does not cause disease when transmitted by transfusion as the period of viraemia is short and like hepatitis A, and unlike the other viral diseases described above, there is no carrier state, so the risk of transmission by blood is small.

In conclusion, screening tests are routinely performed on blood donations to exclude blood donors infected with HBV and HIV. Certain donations will be tested for CMV and the introduction of screening for HCV is imminent despite uncertainty as to how many cases of PTH it will prevent. In the UK, the introduction of HTLV-1 screening is not felt to be justified at present and the introduction of screening for other viruses such as hepatitis A, EBV and parvovirus B19 is very unlikely. Although in theory the introduction of this panel of screening tests would appear a straightforward matter, the current restriction in funds for new developments in health care in the UK, the shortages of trained technical manpower and requirements to integrate the testing of up to 1000 units of blood within a 24 hour period in busy Transfusion Centres makes this a challenging task. Nonetheless, blood transfusion is safer today than ever before, despite the daunting list of transfusion transmitted viral infections.

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