Xenotropic murine leukemia virus–related virus (XMRV) and blood transfusion: report of the AABB interorganizational XMRV task force

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In October 2009, a report in the journal Science identified evidence of infection with the retrovirus xenotropic murine leukemia virus–related virus (XMRV) in the blood of two-thirds of 101 patients diagnosed with chronic fatigue syndrome (CFS) and in 3.7% of 218 healthy control subjects. This was not the first report of XMRV nor the first association of these viral sequences with human tissue. However, because this study recovered virus from lymphocytes, these findings raised concerns anew about a possible pathologic role of XMRV and its potential transmission by blood transfusion. As a result of this publication, in December 2009 the AABB (formerly American Association of Blood Banks) established an Interorganizational Task Force composed of representatives of blood collectors, government agencies, and not-for-profit organizations dedicated to CFS research and policy, supplemented with additional scientific consultants. The Task Force was charged with reviewing the available data on XMRV, recommending action to assess and if necessary mitigate the risk of transmitting XMRV through blood and cellular therapy products, and advising AABB about informing donors, recipients, physicians, and the general public regarding the risk of XMRV transmission.

CHARACTERISTICS OF XMRV

XMRV is a member of the Gammaretrovirus genus of the Orthoretrovirinae subfamily of Retroviridae with high sequence similarity to endogenous murine leukemia viruses. XMRV was so named because its envelope gene was similar to that of xenotropic murine leukemia virus (MLV), an endogenous MLV that infects cells from non-mouse species including humans. Similar agents are found in a wide range of mammalian species and include the porcine endogenous retrovirus, the feline leukemia virus, the koala retrovirus, and the gibbon ape leukemia virus. Although XMRV has been portrayed by some as an AIDS-like virus, this description is not accurate. Gammaretroviruses are much simpler than the complex deltaviruses such as human T-lymphotropic virus (HTLV), or the complex lentiviruses such as human immunodeficiency virus (HIV). The XMRV genome includes gag, pol, and env genes but no accessory or regulatory genes. As the name implies, XMRV is believed to have originated in mice and is the first agent of its class to be identified in humans; it likely evolved as a result of a recombination event between polytropic and xenotropic MLV. Its pathogenic potential in humans is unknown.

The XMRV virions consist of an envelope, a nucleocapsid, and a nucleoid. The virions are spherical to pleomorphic and measure 80 to 100 nm in diameter. The genome is a dimer of linear, positive-sense, single-stranded RNA, approximately 8300 nucleotides long. XMRV is resistant to many of the antiretroviral drugs used to treat HIV-1 infection, but is sensitive to a subset of these inhibitors in vitro. The divergent drug sensitivity profiles of XMRV and HIV-1 are partially explained by specific amino acid differences in their respective protease, reverse transcriptase (RT), and integrase sequences. As
an enveloped retrovirus, XMRV should be susceptible to heat, detergents, and many disinfectants. A photomicrograph of XMRV virions is provided in Fig. 1.

Although little is known about XMRV infectivity, tissue tropism, in vivo reservoirs, and persistence in humans, preliminary information has been obtained from an animal model. Five rhesus macaques inoculated intravenously with XMRV developed transient, low-level viremia between Day 4 and Day 21. Villinger et al. reported at the First International Workshop on XMRV in September 2010 (http://www.virology-education.com/index.cfm/t/Workshop_material/vid/1A5D65BD-FB8B-8AE1-5E10829372D080B4) that XMRV targeted CD4+ T cells in lymphoid organs, macrophages in lungs, and epithelial or interstitial cells in other organs. Animals sacrificed early showed evidence of viral replication in spleen, lung, lymph node, and prostate tissue. Two animals euthanized at 19 weeks after XMRV reinoculation showed wide dissemination of XMRV DNA and RNA including in the gastrointestinal and reproductive tracts as well as in the vaginal tissue of the one female animal. All three chronically infected animals developed antibody responses to env and gag proteins by Western blot assays. No animal developed evidence of illness more than 8 months after inoculation.

Fig. 1. Transmission electron microscope image of XMRV courtesy of Dr John Hackett Jr. (Abbott Diagnostics, Abbott Park, IL).

TESTING FOR XMRV

Research studies on XMRV have employed a number of different assays including the polymerase chain reaction (PCR) assay (nested and real-time PCR) and fluorescence in situ hybridization for direct detection of the viral sequences; serologic assays for detection of circulating antibodies against XMRV include flow cytometry, Western blot and chemiluminescent immunoassays and enzyme-linked immunoassay techniques; immunohistochemical assays have been used for direct detection of viral proteins; and cell culture assays used for detection of infectious virus. It has been difficult to compare assay results from different laboratories due to differences in primer pair or antigen selection, assay reaction conditions, specimen type, and specimen preparation and storage conditions. Currently, commercial high-throughput assays are under development; validation of these assays will be critical for large-scale epidemiologic studies. At this stage of assay development, there are no FDA-licensed diagnostic or blood donor-screening assays.

The U.S. Department of Health and Human Services has established the Blood XMRV Scientific Research Working Group to evaluate XMRV nucleic acid and antibody assays, establish prevalence of XMRV in blood donors, determine if XMRV is transfusion-transmitted, and if so, whether transfusions are associated with any recipient disease. As a first step, the Working Group has established analytical panels and evaluated the performance of its six participating laboratories in detecting XMRV nucleic acid in whole blood, peripheral blood mononuclear cells (PBMCs), and plasma samples spiked with known concentrations of a single XMRV isolate. The next step involves pilot clinical studies that will compare results from whole blood, PBMC specimens, and plasma to investigate methods of collection, processing, freezing, and other issues related to sample preparation and storage. These studies will allow preparation of clinical panels to evaluate assay performance on pedigreed clinical samples including well-characterized negative controls. Once assay methods are optimized at the participating laboratories, testing of coded panels of blood samples obtained primarily from healthy blood donors and from CFS patients can be performed to determine the prevalence of XMRV sequences and seropositivity.

XMRV EPIDEMIOLOGY AND DISEASE ASSOCIATIONS

Evidence of human infection with XMRV was first reported in 2006 when genome sequences from a previously undescribed gammaretrovirus, XMRV were detected in a cohort of US men with localized prostate cancer undergoing radical prostatectomy. The investigators proposed that these men expressed a homozygous mutation
(R462Q) of the antiviral enzyme RNase L rendering them susceptible to infection by this virus and to its possible oncogenic potential. An alternative interpretation might conclude that immune suppression permitted persistence of commensal agents unrelated to the pathogenesis of the tumor. A subsequent study detected XMRV DNA by RT-PCR in 6% of prostate cancer specimens irrespective of the RNase polymorphism and serologic evidence of viral proteins in 23% of 334 specimens using antisera directed against XMRV; no such antibodies were detected in the plasma of seven healthy controls. In contrast, no XMRV was found in 139 Irish prostate cancer patients with the RNase L mutation and studies in a German tissue samples from men without prostate cancer. AU S samples from nonfamilial prostate cancer and in 1 of 70 specific sequences were detected in only one of 105 tissue agreement. In summary, there is no clear explanation for discrepancies in time of infection or prevalence in different studies, PCR analysis revealed no XMRV DNA in 186 samples from CFS patients using real-time PCR for XMRV and related MLVs having sensitivities of 16 copies per reaction. In the other study, stored cells and plasma from two separate CFS cohorts involving 170 patients as well as 395 non-CFS patient controls, of which 157 were blood.

XMRV has also been associated with CFS (also referred to as CFS-myalgic encephalitis), a debilitating disorder characterized by persistent fatigue of at least 6 months’ duration and a constellation of other symptoms, including postexertional fatigue after even modest physical or mental activity. Chronic inflammation and abnormalities of the immune and endocrine systems have been documented. Because modulation of RNase L activity also has been reported in subsets of CFS patients, samples from CFS patients were examined for evidence of XMRV. The previously cited study in the United States identified proviral DNA of XMRV in PBMCs from patients suffering from CFS. In 68 of 101 CFS patients (67%), but also in eight of 218 (3.7%) healthy controls, XMRV could be detected by a variety of methods including PCR and co-infection of susceptible cell lines using either patient-derived activated PBMC or plasma samples. (Table 1). Plasma from nine of 18 CFS patients contained antibodies that reacted with envelope protein from a virus that cross-reacts with XMRV; no such antibodies were detected in the plasma of seven healthy controls.

In contrast, XMRV was not detected in two independent studies of clinically well-characterized symptomatic CFS patients in the United Kingdom. In one of these studies, PCR analysis revealed no XMRV DNA in 186 samples from CFS patients using real-time PCR for XMRV and related MLVs having sensitivities of 16 copies per reaction. In the other study, stored cells and plasma from two separate CFS cohorts involving 170 patients as well as 395 non-CFS patient controls, of which 157 were blood.

### TABLE 1. Comparison of published XMRV studies in patients with CFS

| Study | + CFS patients (%) criteria | + Controls (%) source | Sample source | Assays | Patient selection |
|-------|---------------------------|----------------------|---------------|--------|------------------|
| Lombardi et al. | 68/101 (67) NAT | 9/18 (50) serology Fukuda, Canadian | 8/218 (3.7) 0/7 serology subjects undergoing routine medical testing | Activated PBMC plasma | Nested PCR serology gag culture | 25 patients Incline village NV and 76 sporadic cases in United States |
| Erlwein et al. | 0/186 Fukuda | NT | | PBMCs | Nested XMRV, MLV PCR | UK patients with CFS |
| Groom et al. | 0/142 NAT 1/28 serology Fukuda criteria | 0/395 NAT 25/395 (6.3) serology; only 1/28 from a CFS patient | | PBMCs | Nested PCR (gag) Real time-PCR env Viral neutralization | Two UK cohorts with CFS |
| Van Kuppeveld et al. | 0/32 NAT Sharpe | 0/43 NAT matched neighborhood control | | PBMCs | Nested PCR (gag) Real time-PCR (int) | Netherlands matched case-control study |
| Switzer et al. | 0/51 NAT, WB, ELISA, IFA Reeves 2005 | 0/53 0/41 serology healthy US blood donors | | PBMC plasma Nested PCR, WB, ELISA, IFA tested in three labs | Survey-identified patients from Georgia and Wichita, KS |
| Lo et al. | 32/37 (86.5) NAT MLV-like virus Fukuda criteria | 3/44 (6.8) MLV-like virus US blood donors | | PBMC plasma | Nested PCR gag and env | CFS cohort followed in Boston clinic |
| Hong et al. | 0/65 Fukuda criteria | 0/85 Chinese blood donors—65 healthy, 20 infected with HBV, HCV, HIV, HTLV | | PBMC plasma | Multiplex RT-PCR; RT-PCR | Chinese cohort of CFS patients from Peking Medical College Hospital |

* Correction added after online publication 14-Jan-2011. Nat and serology numbers have been updated.*
donors, found no XMRV sequences corresponding to two different env regions. Twenty-six (4.6%) of the 565 serum samples contained antibodies that could neutralize XMRV; however, only one of these was from a CFS patient. Most of these antibody-positive specimens were able to neutralize similar viruses, indicating significant cross-reactivity. PBMC cryopreserved in 1991 to 1992 from a Dutch cohort of 32 CFS patients and 43 healthy controls were tested by real-time PCR targeting the integrase gene and/or a nested PCR assay targeting the gag gene and having a sensitivity of 10 XMRV sequence copies per 10^5 PBMCs. No XMRV sequences could be detected in any sample. A US study conducted by the Centers for Disease Control and Prevention (CDC) tested archived blood specimens from persons with CFS diagnosed with the revised 1994 CDC case definition and matched healthy controls from Wichita, Kansas, and metropolitan, urban, and rural populations in Georgia. Nested PCR testing with a sensitive gag and a pol nested PCR assay of DNA specimens from 51 CFS patients, 56 healthy controls, and 41 US blood donors were all negative. Using a Western blot that showed excellent sensitivity to MLV and XMRV antibodies and 100% specificity in a limited evaluation (i.e., no reactivity on sera from 121 US blood donors and 26 HTLV- and HIV-infected sera), plasma from 51 CFS cases, and 53 healthy controls all tested negative. Negative results were confirmed by two external laboratories. A study of 65 Chinese patients with CFS followed at Peking Union Medical College and 85 blood donor controls matched for age, sex, and place of residence failed to identify XMRV with highly reproducible real-time PCR and RT assays sensitive to 20 copies per reaction and 10 IU/mL, respectively. In contrast, in a study from FDA and NIH laboratories of archived specimens from well-characterized CFS patients and volunteer blood donors, analysis of the amplified gag gene sequences revealed a genetically diverse group of MLV-related sequences (polytropic MLV). On phylogenetic analysis the cluster is clearly separable from the cluster formed by the newly reported XMRVs. These results show an association between the presence of MLV-like virus gene sequences in blood and PBMC-derived DNA samples from CFS patients, 32 of 37 (86.5%), compared with three of 44 (6.8%) healthy blood donors. Seven of eight gag-positive patients tested positive when a subsequent fresh sample was obtained nearly 15 years later. As expected, sequence diversity was observed in the later samples. Since the gag gene sequences identified in this study share 96.6% homology with XMRV, these results have been interpreted by some as confirming those of the originally reported positive CFS study, while others find these differences confounding. At the First International XMRV Workshop sponsored by NIH in September 2010, a laboratory at Cornell University reported finding similar MLV gag sequences in eight (80%) of the 10 CFS patients meeting the 1994 CDC case criteria and three (30%) of 10 individuals who had recovered from CFS, compared to one (10%) of 10 healthy control subjects. This report establishes the third independent group to detect MLV sequences in CFS patients.

Among related findings are those recently reported by investigators in Germany that XMRV could be detected in respiratory secretions. In this study, 267 respiratory samples taken from German patients were screened for XMRV infection by PCR assay. The prevalence of XMRV DNA was 2.3% (3/135) in travelers from Asia who had respiratory tract infections, 3.2% (1/31) in patients with chronic obstructive pulmonary disease, 9.9% (16/161) in immunosuppressed patients with severe respiratory tract infections, and 3.2% (2/62) in the healthy control group. The finding that XMRV infects the respiratory tract does not prove that the virus can be transmitted by the respiratory route as retroviruses are not usually spread by respiratory secretions. Tests for the presence of XMRV in samples obtained from men at risk for HIV infection, HIV-positive men, patients with amyotrophic lateral sclerosis, adults with spondyloarthritides, and children with idiopathic infectious diseases have been reported as negative in limited studies.

The reasons for the discordant findings in the several studies of prostate cancer and CFS are not clear. There may be differences in the cohorts studied, which are drawn from different geographic areas, or in the selection of individual patients within cohorts in terms of disease acuity, chronicity, severity, and duration. The assay procedures, including the use of appropriate positive and negative controls, sample source, sample preparation, and sample storage differ among the studies (Table 1). Given that viral load appears to be low, these variables could impact XMRV detection. Further, it is becoming clear that XMRV belongs to a family of related viruses with small, but potentially significant, genetic variations which are likely to emerge over time. As a result, sequence variation may complicate detection by different assays.

An important concern regarding the discrepant study findings involves the reliability and consistency of the criteria to make a diagnosis of CFS and to select subjects for inclusion in CFS research studies. Estimates of the number of affected individuals vary widely, from 1 to 4 million Americans to 17 million people worldwide. The most widely used CFS case definition for research follows the Fukuda criteria published by an international study group led by CDC in 1994. This definition is based on clinical criteria in which patients are required to exhibit persistently disabling fatigue of at least 6 months’ duration accompanied by at least four of a possible eight symptoms. The 2003 Canadian Clinical Consensus Criteria provides more specific symptom definition, but was intended for application in clinical settings and has not been used broadly to define research cohorts. Both definitions have been criticized for containing vaguely
XMRV and Blood Transfusion

Does XMRV pose a risk to transfusion recipients? Given that XMRV is a retrovirus and appears to be present in PBMNCs and in plasma, blood transmission, although undocumented, is plausible. This possibility is supported by the demonstration that human cells have been infected in the laboratory by virus found in human specimens and by the transfection transmissibility of other retroviruses (e.g., HIV and HTLV).1 Related viruses are oncogenic and immunosuppressive in different animal species, and XMRV has been shown to infect lymphoid cells and to disseminate to other tissues in the rhesus macaque model.5

At present, information regarding the prevalence of XMRV in either patient populations or volunteer donor populations remains fragmentary and controversial. The identification of gammaretroviruses in volunteer donors suggests that there are asymptomatic chronic carriers. Long-term persistence of MLV-like virus has been reported in some symptomatic patients for as long as 15 years.18 Few transfusion transmission–related data are available; however, the available published epidemiologic data do not link the incidence of CFS or prostate cancer to receipt of a blood transfusion. In a recently conducted Web-based survey of 1529 individuals self-reporting a diagnosis of CFS, 8% (124) indicated that they had received a blood transfusion before becoming ill, while 3% (50) reported transfusion after being diagnosed with CFS. Of those having reported being a blood donor, 225 (14.7%) reported having donated in the past 10 years and 115 (7.5%) indicated that they had given blood since becoming ill with CFS.31 Regardless, there is no evidence of any increased risk of CFS in hypertransfused individuals such as persons with hemophilia or patients with thalassemia. There is little information regarding potential animal reservoirs or mechanisms of transmission. Consequently, no donor risk factors for XMRV infection have been identified. If infection through transfusion does occur, the incubation period, viral kinetics, persistence of the virus in the circulating blood, or in stored blood (fresh, refrigerated, cryopreserved) need to be investigated.

There are no published data concerning the effectiveness of leukoreduction filters in removing XMRV from blood, although given the probable presence of the agent in plasma, filtration would not likely prevent transmission. Pathogen reduction technologies used in the preparation of plasma fractions would be expected to inactivate XMRV, since most methods effectively reduce enveloped viruses to undetectable levels. A preliminary report suggests that at least one manufacturer’s commercial pathogen inactivation technology achieves robust reduction of spiked XMRV in single-donor platelets and red blood cells.32

Several assays for direct detection of XMRV and for serologic detection of exposure to XMRV are in use in research laboratories; efforts to standardize these assays are well under way (see above), and there is commercial interest in developing diagnostic nucleic acid testing (NAT) and serologic assays for licensure. However, no approved blood screening test is available and no studies are yet under way to license any assay for blood donor screening purposes. Most importantly, since no causal association of XMRV with human disease has been demonstrated, a decision to introduce a blood donor screening assay, were one to become available, would appear to be premature. Many viruses (e.g., GVB-C, the TTV group) are known to be transmitted by transfusion without evidence of pathologic effect.

On May 10, 2010, the CFS Advisory Committee recommended to the Secretary of Health and Human Services that, “Given the concerns for patient health, that the Secretary ask the government and non-government organizations responsible for the US blood supply to indefinitively defer individuals with a current or past history of CFS from donating blood and that a screening question about CFS be asked of all donors.” The CFIDS Association of America has long advised patients against donating blood or organs.33 At present there is no FDA-required question concerning XMRV or CFS. Current donor eligibility criteria require that prospective blood donors answer a screening question confirming that they feel well on the day of donation. This should exclude some subjects with symptomatic CFS. Prospective donors with a history of cancer are commonly deferred for a variable period of...
time (depending on the blood center) unless exempted by the medical director.

On June 18, 2010, the AABB issued an Association Bulletin to its membership advising that medically diagnosed CFS patients be discouraged from donating blood. The bulletin stated that, as an interim measure, and until further definitive data are available, AABB recommends that blood-collecting organizations make educational information available regarding the reasons why an individual diagnosed with CFS should not donate blood or blood components. The American Red Cross and a number of independent blood centers have implemented this recommendation and are monitoring response to these educational materials. Early experience in Canada and the United States suggests that the rate of reporting medically diagnosed CFS will be low. The data currently available from those studies reporting positive results suggest a lower prevalence of XMRV associated with prostate cancer (0%-27%) than with CFS (0%-86.5%). There is no recommendation to change the deferral criteria for potential blood donors with a history of prostate cancer, who should continue to be evaluated according to current donor criteria relating to a history of cancer. At the present time, there is no requirement to perform recipient tracing (i.e., lookback) studies for those donors who report a diagnosis of prostate cancer or a diagnosis of CFS. It is possible that limited lookback investigations will be conducted in a research setting.

The AABB Task Force has developed materials in the Association Bulletin that blood-collecting organizations may wish to utilize as provided or alter to better conform to the needs of local donor populations. The resources provided include the following and can be accessed on the AABB Web site at http://www.aabb.org.

- A statement that blood-collecting organizations can make available to potential donors in the form of a poster or handout, which requests that individuals diagnosed with CFS by their physician not donate.
- An educational handout that blood-collecting organizations can make available to potential donors who request more information regarding why those with CFS should not donate.

The AABB bulletin did not recommend the use of a specific donor question since many of the symptoms of CFS are common and vague. Hence, a specific donor screening question that is not carefully crafted could result in substantial donor loss. Likewise, given the absence of other known risk factors for XMRV infection, symptom-based questions would not identify asymptomatic infections that might prove to be frequent and/or transmissible. Donor deferral policies have been implemented by Canadian Blood Services, the Australian Red Cross, the New Zealand Blood Services, and the UK National Health Service Blood and Transplant that require deferral when a donor volunteers a history of CFS; no specific questions are being posed.

**FURTHER AABB ACTIONS**

The AABB Board of Directors and the AABB Interorganizational Task Force on XMRV will continue to monitor activity and research associated with XMRV and, as appropriate, will provide further communication and guidance to the blood banking and transfusion medicine community. The AABB Interorganizational Task Force on XMRV has identified the need to involve representatives of organizations that engage in tissue and organ donation and transplantation in discussions of precautions regarding XMRV. Recently, a separate Interorganizational Task Force was formed to evaluate the unique considerations for cell-based therapies. Membership includes representation from American Society for Blood and Marrow Transplantation (ASBMT), American Society for Apheresis (ASFA), CFIDS, FDA, and the National Marrow and Donor Program (NMDP), as well as a European member of the cellular therapy community since many cellular-based products cross international borders, and the CFIDS Association of America. Additional information can be found on the XMRV Fact Sheet that is updated regularly on the AABB Web site.

**FUTURE STUDIES**

Studies of XMRV are in their early stages and the importance of this agent to recipients of blood transfusions has not been determined. The availability of validated assays will make it possible to undertake large-scale epidemiologic surveys, to identify infected blood donors, and to trace their previously donated units and evaluate their recipients. It also will be possible to investigate heavily transfused populations such as patients with hemoglobinopathies and inherited disorders of hemostasis who receive both plasma fractions and single donor blood components. Other target populations include immunodeficient or heavily immunosuppressed patients who receive blood transfusions, cellular therapies, or organ transplants. Investigating the natural history of infection in asymptomatic carriers of the virus will be more difficult and require prolonged follow-up.

If XMRV is present in normal donors and transmitted by blood, it will be important to define the efficiency of infection, the NAT-negative window period, the serologic window, the percentage of patients who develop antibody after exposure, and the persistence of virus and antibody response. Age-adjusted prevalence and true incidence are important in determining whether this is a truly “emerging” agent, and if so, how rapidly, by what mechanisms of transmission, and in which populations it is
spreading. Further studies should determine whether there is genetic susceptibility to infection, viral persistence, and clearance.

The most pressing issue is whether XMRV/MLV is causally related to CFS or to any illness. Patients infected with hepatitis C virus may be asymptomatic for decades, yet eventually develop cirrhosis, end-stage liver disease, and hepatocellular carcinoma. If XMRV/MLV is pathogenic, a similar long latency is conceivable. Additional studies should clarify the infectivity of the agent(s) under different component storage conditions, their removal by filtration, and their sensitivity to different pathogen inactivation technologies.

XMRV may represent another emerging infectious agent that poses a risk to transfusion safety. As with other agents, it is imperative that action taken on behalf of blood safety be expeditious, yet based on the best available science. Currently, the scientific data are incomplete and conflicting. With the development of validated assays, additional data will become available in the near future and these data will help inform decisions on blood donor eligibility and screening.

CONFLICT OF INTEREST

None.

APPENDIX

Interorganizational task force on XMRV personnel

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