

Encephalitis Caused by Pathogens Transmitted through Organ Transplants, United States, 2002–2013

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

More than 500,000 solid organ transplants have been performed worldwide, and more than 28,000 are performed annually in the United States. Improvements in immune-modulating therapy, critical care medicine, and surgical techniques have led to the increased success of organ transplantations, and more patients are now eligible for these procedures.

The risk for infections caused by pathogens transmitted through solid organ or tissue transplants, referred to here as donor-derived or transplant-transmitted infections, has been recognized for decades and remains a worldwide public health problem. Because of immunosuppression and underlying co-existing conditions in transplant recipients, infections can be severe and fatal. The recognition of this risk led to the screening of donors for some infectious agents, such as, HIV, which made the organ supply substantially safer. However, a residual transmission risk persists, which might be further reduced by the use of new technologies, such as nucleic acid testing, or NAT.

Since 2002, several types of emerging donor-derived infections have been reported with increasing frequency among solid organ transplant recipients seeking medical care for encephalitis. These cases can present a diagnostic challenge for clinicians and highlight the need to increase awareness among transplant clinicians regarding the necessity for prompt recognition and treatment of transplant-transmitted infections.

Since 2002, the Centers for Disease Control and Prevention has investigated clusters of encephalitis among transplant recipients. Cases have been caused by emerging pathogens, including West Nile virus, rabies virus, lymphocytic choriomeningitis virus, and *Balamuthia mandrillaris* amebae. The cases highlight the difficulties in diagnosing or recognizing clusters of infectious encephalitis among transplant recipients.

West Nile virus was historically associated with infrequent epidemics of relatively mild febrile illness. In 1999, West Nile virus was first identified in North America, where it caused an outbreak of encephalitic illness in New York City. Within 5 years it became the most common etiologic agent of arboviral encephalitis in the Western Hemisphere.

In 2002, several cases of serologically confirmed West Nile virus infection occurred in persons with little or no known exposure to mosquitoes, and epidemiologic evidence suggested transmission of the virus through blood transfusions. Later that year, the first recognized U.S. cases of organ transplant–transmitted West Nile virus were described. For these infections, the initial link to the transplanted organ was made by histopathologic evaluation and immunohistochemical testing of tissue from an organ recipient who died 4 weeks after undergoing transplantation. Laboratory and epidemiologic data substantiated this mode of virus transmission and documented that the organ donor had likely acquired West Nile virus through a blood transfusion. Subsequent investigation by CDC verified 23 cases in 2002 of West Nile virus acquired through blood or blood components.

It is believed that West Nile virus transmission through blood transfusion has become rare since nucleic acid testing of donated blood was implemented; however, this may not be the case in the solid organ–transplant setting because organ donor screening has not been mandated.

Six clusters of organ transplant–transmitted West Nile virus were reported to CDC during 2002 to 2013. In those clusters, West Nile virus infection developed in 12 of 16 transplant recipients; encephalitis developed in 9 of the 12 infected persons, and 4 of those 9 patients died. It is likely that signs and symptoms of encephalitis among transplant recipients during a West Nile virus outbreak led to the recognition that West Nile virus had been transmitted through organ transplants.

It may be that transmission is possible because of viral persistence in donated organs after peripheral viremia has cleared or because of intermittent viremia from a reservoir organ, such as a kidney. Therefore, it may prove challenging to implement West Nile virus screening of potential organ donors.

Rabies virus is an enveloped, negative, single-stranded RNA virus. It is nearly always fatal once neurologic signs develop.

The transmission of rabies virus through cornea transplantation has been described, but transmission through solid organ transplantation was not recognized before 2004. In July 2004, CDC was notified that 3 recipients of solid organs and 1 recipient of an iliac artery segment from a common donor had died from encephalitis, which was eventually found to be caused by rabies virus infection.

In 2013, another case of transplant-transmitted rabies was identified in the United States. A raccoon rabies virus variant was identified in the organ donor and the infected recipient. Signs and symptoms of rabies developed in the organ recipient around 17 months after the transplantation. Three unvaccinated recipients of organs from the same donor remained asymptomatic.

Lymphocytic Choriomeningitis Virus, or LCMV, disease is an uncommon, primarily rodent borne infection that occurs among people who have substantial contact with infected small rodents. Infection in immunocompetent people is believed to be asymptomatic, and it is generally mild and self-limited in people in whom clinical disease develops. Severe meningoencephalitis has been reported among immunocompromised patients.

In 2003 and 2005, CDC investigated clusters of meningoencephalitis among solid organ transplant recipients in the United States. The 2003 cluster occurred among recipients of organs from a common donor from Wisconsin who had died from a subdural hematoma. The 2005 cluster of cases occurred among 4 recipients of organs from a common donor who died from an ischemic stroke. Pathologic investigation and immunohistochemical staining of specimens led to the diagnosis of LCMV infection in the transplant recipients, and epidemiologic investigation showed that the donor had a pet hamster. Although the donor had no evidence of active LCMV infection, the hamster was infected with a strain that was genetically similar to those that infected the transplant recipients.

In 2008, CDC investigated reports of hepatic insufficiency, multi-organ system failure, and death among 2 recipients of kidneys from a common organ donor. Although the recipients had no signs

or symptoms of encephalitis, the donor had aseptic meningitis at death and was retrospectively found to have serum antibodies against LCMV.

Another cluster of infections with a novel LCMV-related virus among 3 organ transplant recipients was reported in Australia; the patients died of encephalitis within 6 weeks of undergoing transplantation. The donor, who died of a hemorrhagic stroke, had serologic evidence of recent LCMV infection and had recently traveled to rural southern Europe, where he may have been exposed to rodents.

Balamuthia mandrillaris, a species of small, free-living, aerobic amebae, has been reported as a cause of granulomatous amebic encephalitis. *Balamuthia mandrillaris*-associated skin lesions have been described, and untreated infection can progress to fatal encephalitis. Neurologic disease is characterized by the presence of single or multiple space-occupying intracranial lesions that cause a variety of focal and diffuse neurologic signs and symptoms. *Balamuthia mandrillaris*-associated encephalitis is almost always fatal, even with treatment. Diagnosis has traditionally required culture of the organism or identification of amebic trophozoites or cysts from biopsy samples of affected tissue; however, a real-time PCR for use with cerebrospinal fluid samples is available.

Infection with transplant-transmitted *Balamuthia mandrillaris* amebae was first identified by CDC in 2009 following reports by clinicians in Mississippi of encephalitis among 2 recipients of kidneys from a common donor. A second cluster of infections with transplant-transmitted *Balamuthia mandrillaris* amebae was reported to CDC in 2010. In this cluster, encephalitis developed in 2 organ transplant recipients in Arizona.

The transplant-transmitted cases of encephalitis we described highlight several important diagnostic and clinical challenges related to the recognition and treatment of certain emerging infections. The precise rate of donor-derived transmission of West Nile virus, rabies virus, lymphocytic choriomeningitis virus, and *Balamuthia mandrillaris* amebae that cause encephalitis among transplant patients is not known, but such cases are rare and may not be immediately recognized by clinicians. Diagnosis is further complicated because of laboratory screening limitations for some of these pathogens. Moreover, few effective treatment options are available once patients exhibit signs or symptoms of infection. However, there is limited evidence that prophylaxis or treatment, even for asymptomatic transplant recipients, may be effective following exposure to these pathogens. Identification of possible infectious encephalitis among organ donors and establishment of proactive notification systems for transplant centers is crucial. Furthermore, surveillance systems for possible donor-derived infectious encephalitis could reduce illness and death among organ transplant recipients.

Several difficulties are inherent in the identification and diagnosis of possible transplant-transmitted encephalitis. The hallmark clinical features of encephalitis, such as, fever and altered mental status, are common in severely ill hospitalized patients, including people who've undergone organ transplantation. Differentiating between encephalopathy caused by a severe underlying injury or illness and transplant-transmitted infection may be clinically challenging. Organs from a single donor are transplanted to recipients in multiple centers, frequently in widely separated geographic areas. Linking fever and encephalitis in transplant recipients to an infectious pathogen transmitted from a common donor may be relatively easy if all recipients are in the same hospital. However, if recipients are located in widely dispersed geographic areas, this linkage may not be recognized.

Further complicating organ safety in the United States is the regulatory oversight of solid organs. Although some policies are set by the Health Resources and Services Administration through the Organ Procurement and Transplantation Network, and infectious disease guidelines are available, screening of potential organ donors is under the purview of the individual organ procurement organizations, and variability exists in the testing that is performed for many agents. No organ procurement organization currently screens for all of these diseases discussed in this review. Given that the diseases are rare, laboratory screening of all donors is unlikely to be cost effective. However, introduction of a standardized risk assessment tool to gather medical, demographic, and social risk factors for infectious encephalitis from all organ donors may reduce the risk of transmitting infectious pathogens to transplant recipients.

There is a need for a national system for rapid communication on disease clusters, particularly infectious encephalitis, involving organ and tissue recipients from a common donor. Given that prevention and treatment options are available, recognition of donor or recipient infection, even after transplantation, could improve clinical outcomes among recipients.

Availability of appropriate samples to test is also a critical issue. The Retrovirus Epidemiology Donor Study Allogeneic Donor and Recipient repository, which was previously instituted in the blood transfusion community, could serve as an example of potentially effective surveillance linking organ donors and recipients. Such a repository, with voluntary participation, if linked with a surveillance system for transplant-transmitted encephalitis could obviate difficulties related to specimen availability and laboratory testing, facilitate diagnosis, better inform clinical management, and guide policy decisions related to organ donor guidelines. All of the emerging infections described in this review were initially recognized by histopathologic evaluation and immunohistochemical testing of both autopsy and biopsy tissues. Increased rates of autopsy among organ donors could enable the identification of new and emerging infections in transplant recipients. Prompt notification to public health authorities can enable rapid investigation and discovery of clusters from a common donor. Until active surveillance can be implemented, timely communication and use of traditional and novel diagnostic testing can be crucial in identifying unusual and emerging infections caused by transplant-transmitted pathogens.

I'm Dr. Mike Miller, for *Emerging Infectious Diseases*, and I've been reading an abridged version of the article Encephalitis Caused by Pathogens Transmitted through Organ Transplants, United States, 2002 to 2013. You can read the entire September 2014 article online at cdc.gov/eid.

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