Protocol That Saved Life of a Rabies Patient Requires Further Study

BY SHARON WORCESTER
Tallahassee Bureau

The doctors who treated the first known patient to survive rabies without prior vaccination have published their aggressive and previously untested treatment protocol, but they caution that it requires further study.

"Clearly, our experience with this patient requires replication in other patients and proof-of-concept experiments in animal models," said Rodney E. Willoughby Jr., M.D., of the Medical College of Wisconsin, Milwaukee, and his colleagues.

©AP/WIDE WORLD PHOTOS

Jeanna Giese, 15, in wheelchair, with her father John Giese, was discharged after undergoing experimental treatment for rabies.

The 15-year-old patient developed confirmed clinical rabies 1 month after being bitten on the left index finger by a bat. She was treated with a strategy that involved induction of therapeutic coma, and antiexcitatory and antiviral drug therapy under supportive intensive care. The concept was to protect the brain from injury while allowing the launch of a natural immune response against the virus (N. Engl. J. Med. 2005;352:2508-14).

The patient was treated with ketamine, midazolam, ribavirin, and amantadine. Doses were adjusted as needed due to responses and probable drug-related toxicities, which included hemolysis, pancreatitis, acidosis, and hepatotoxicity. She did not receive rabies vaccine or rabies immunoglobulin because she demonstrated immune response and because of concern regarding harm from a potentiated immune response, the investigators noted.

On the eighth day of hospitalization, a lumbar puncture indicated an increased level of rabies antibody, and sedation was tapered. On hospital day 31, the patient was determined to be cleared of transmissible rabies, and was removed from isolation.

She was discharged to home on hospital day 76. At a follow-up visit 131 days after her initial hospitalization, the patient was progressing, and had returned to school part time. She continues to experience dysarthrotic speech, buccolingual choreoathetosis with generalized choreoathetosis and intermittent dystonia and ballismus, which affect her gait and fine-motor skills, Dr. Willoughby and his associates said.

Prior to this case, five cases of survival following rabies had been well documented, but all received occupationally related preexposure rabies vaccination or postexposure prophylaxis; this is the first known patient to survive with only naturally acquired immunity.

It should be noted that the patient was young and athletic, and may have received a limited quantity of inoculum, the investigators stressed, adding that because the bat was not recovered, it is unclear if the patient's survival was due to an "unusual, more temperate or attenuated variant of the virus, or a rare host polymorphism."

"Therapy may have been more effective than in past cases because of the inferred limited exposure to rabies virus, early recognition of the disease, and aggressive management," the investigators said, noting that the survival of this patient doesn't change the fact that rabies has the highest case fatality ratio of any infectious disease. ■

Single Donor Tied to Organ Recipients After Rabies Deaths

Rabies caused encephalitis that killed four transplant recipients within 50 days of receiving organs from a common donor, the Centers for Disease Control and Prevention has reported.

Only during the postmortem investigations was it discovered that a bat had bitten the male donor before he died, said Arjun Srinivasan, M.D., and his associates (N. Engl. J. Med. 2005;352:1103-11).

Four days before dying, the donor was seen twice in an emergency department for nausea, vomiting, and difficulty swallowing. He was then admitted to another hospital with altered mental status requiring intubation, fever of 100.5° F, and systolic blood pressure more than 200 mm Hg.

A toxicology screen was positive for cocaine and marijuana. Imaging showed an ongoing subarachnoid hemorrhage that eventually led to seizures, coma, and brain death.

No donor screening tests had indicated any danger of infectious disease.

Two patients each received one kidney, and a third received the liver. Within 30 days, all developed progressive encephalitis with rapid neurologic deterioration (agitated delirium and seizures) followed by respiratory failure within 48 hours. Death followed 7-23 days after onset of neurologic symptoms.

CNS tissue specimens obtained at autopsy showed characteristic signs of rabies—Negri bodies, particularly in the Purkinje cells of the cerebellum and neurons in the frontal cortex, thalamus, hippocampus, midbrain, and pons.

Suckling mice inoculated with cultures of tissue suspension and cerebrospinal fluid died or developed neurologic abnormalities within 7-10 days.

Furthermore, a fourth patient, who had received an iliac artery graft from the infected donor to revise the hepatic artery after liver transplantation, also died from encephalitis.

Symptoms of rabies typically don't develop this quickly, the investigators noted. "It is unknown whether the shorter incubation period was due to the immunosuppression, the route of transmission, or both."

—Michele G. Sullivan

West Nile Virus Doesn't Play by the Rules

BY GWENDOLYN HALL
Associate Editor

MIAMI BEACH — It takes more than a positive serum IgM by enzyme-linked immunosorbent assay to make a definitive diagnosis of West Nile virus encephalitis in a patient with neurologic symptoms, Karen L. Roos, M.D., said at the annual meeting of the American Academy of Neurology.

For example, an elderly patient presents with 4 days of confusion and tremor, and her serum IgM is positive for West Nile virus on enzyme-linked immunosorbent assay (ELISA). Spinal fluid analysis indicates that she has a lymphocytic pleocytosis. Does this patient have West Nile virus encephalitis?

Maybe not. "When I was in medical school, I learned that the IgM was positive early, became negative quickly, and then the IgG became positive. But West Nile is not playing by the rules of medical school," Dr. Roos said.

Serum West Nile IgM level on ELISA can remain positive for 6-12 months or longer after infection, and only 1 in 150 people develop neurologic symptoms from the virus, said Dr. Roos, the John and Nancy Nelson Professor of Neurology at Indiana University, Indianapolis.

Serum IgM level is therefore not sufficient evidence to assume that the patient's neurologic presentation is due to West Nile virus infection. "Don't put a lot of stake in a serum West Nile virus IgM," she said.

The neurologic symptoms of this patient can be definitively attributed to West Nile virus infection if the virus is isolated in tissue, blood, or cerebrospinal fluid or IgM antibody is found in the cerebrospinal fluid. IgM antibody cannot cross the blood-brain barrier, so central nervous system infection should be "strongly suspected" if IgM antibody is found in cerebrospinal fluid.

Also, in the case of West Nile encephalitis or any viral encephalitis or meningitis where the causative virus is unknown, "if you send acute and convalescent titers in patients with viral meningitis or encephalitis, you will very often find the virus," Dr. Roos said. There will be a fourfold increase in IgG antibodies between acute and convalescent serums.

This is not useful for diagnosis during the acute stage, but patients are considerably more able to put up with their headaches and other continuing symptoms in convalescence if they know which virus they had, Dr. Roos said.

In the acute phase, there may be no serum findings, but it may be possible to pin down the virus by demonstrating a stable elevated antibody titer. If serology shows that the patient maintains a stable antibody titer of more than 256 mg/dL, for example, "you can then say that's a presumptive diagnosis," she said. "Realistically, this is the best we can do, sometimes."

In general, IgM or IgG serum antibody titers that are positive for West Nile virus on ELISA should be confirmed by plaque reduction neutralization assay in cell culture to eliminate false positives from cross-reactivity with other flaviviruses—particularly St. Louis encephalitis virus, Dr. Roos said. ■

Hotlines Provide Expert Advice on HIV/AIDS

The National HIV/AIDS Clinicians' Consultation Center at the University of California, San Francisco, offers two telephone services for physicians.

The center's Warmline provides expert consultation on antiretroviral treatments, prophylaxis and management of opportunistic infections, and primary care of patients with HIV/AIDS. The service is available Monday to Friday 8 a.m. to 8 p.m. EST by calling 800-933-3413.

In addition, the center offers advice on occupational exposure to HIV via the PEPline, a clinicians' postexposure prophylaxis hotline, at 888-448-4911. Experts provide around-the-clock advice on managing occupational exposures to HIV, as well as hepatitis B and C.