West Nile Encephalitis

Hema Azad, MD
Sajan Thomas, MD

Since the mid-1970s, emerging infectious diseases in the United States have included AIDS, Ebola virus disease, Lyme disease, ehrlichiosis, dengue fever, and hantavirus pulmonary syndrome. After an outbreak of meningoencephalitis in the New York City area late in the summer of 1999, the West Nile virus was added to this list.[1] West Nile encephalitis, which is caused by the West Nile virus, has gained attention in the United States due to the morbidity and mortality that it caused between the summers of 2002 and 2003. The virus traveled to the United States from an unknown gateway (most likely through trade and commerce), expanded geographically, and persisted in the United States. Most likely, West Nile encephalitis has become a permanent fixture of the United States' medical landscape.[2]

The causative agents of approximately two thirds of presumed viral encephalitis cases in the United States remain unknown. However, herpes simplex viruses, enteroviruses, and arboviruses are the most common causes of acute encephalitis in the United States. Molecular diagnostic techniques, such as reverse transcriptase polymerase chain reaction (RT-PCR), have revolutionized the diagnosis of viral encephalitis.[3] The analysis of the genome of the flavivirus responsible for the New York City 1999 encephalitis epidemic cloned from human brain by RT-PCR indicates its identity as a lineage 1 West Nile virus closely related to West Nile viruses that previously were isolated in the Middle East.[4]

This article briefly reviews the natural history, diagnosis, and treatment of West Nile encephalitis.

EPIDEMIOLOGY

The West Nile virus is indigenous to Africa, Asia, Europe, and Australia. The West Nile virus first was isolated and identified in 1937 from the blood of a woman presenting with mild febrile illness in the Nile district of Uganda.[5] Recently, the virus was introduced to North America, where it was first detected in New York City in the late summer of 1999. Since then, the West Nile virus progressively has extended its range from 1 state in 1999 to 3 states in 2000, 10 states in 2001, 40 states in 2002, and 46 states in 2003. As of 31 March 2004, the Centers for Disease Control and Prevention (CDC) has received reports of a total of 9858 human cases of West Nile virus infection from 46 states, with 264 human deaths in 2003.[6] Epidemiologic data regarding West Nile virus infections for the years 1999 to 2003 are shown in **Table 1**. The West Nile virus also has been detected in south-central Canada. In 2001, West Nile encephalitis was serologically diagnosed in a resident of the Cayman Islands who had no recent travel history; this finding is circumstantial evidence that the virus has entered the Caribbean Islands.[7]

In temperate and subtropical zones, most human infections with West Nile virus occur in summer or early fall. In tropical areas, incidence is greatest in the rainy season as mosquitoes breed in abundance. Although there appears to be no specific age or sex predilection, the incidence of encephalitis and death increases with age. In Australia, only sporadic human cases were caused by Kunjin virus (a subtype of West Nile virus), and encephalitis was rare.[7] In Romania, the 1996 West Nile virus epidemic was transmitted by *Culex pipiens* species of mosquito. All infected sites were heavily infested, including poultry sheds, houses, and especially apartment complexes, many of which had leaking pipes and standing water in their basements.[8] An Egyptian study performed in the 1950s revealed 2 epidemiologic extremes. In an area where the virus circulated for many years, uncomplicated West Nile fever was a mild, common childhood disease that was easily overlooked among many other febrile conditions. In the other area (northern temperate zone), where there was no background immunity, an aging and largely immunologically naive population encountering the virus for the first time had a preponderance for meningoencephalitis.[7]

The risk factors identified for West Nile virus infection are outdoor activity, lack of application of mosquito

Dr. Azad is a resident in internal medicine and Dr. Thomas is assistant program director of the internal medicine residency program, Westlake Hospital, Melrose Park, IL.

repellents, and collection of water around residential areas that serve as breeding grounds for mosquitoes. The 1996 to 1997 outbreak of West Nile fever in and near Bucharest, Romania, with more than 500 clinical cases and a case-fatality rate approaching 10%, was one of the largest outbreaks of arboviral infection in Europe. This latest outbreak reaffirmed that mosquito-borne viral diseases can occur on a mass scale even in temperate climates.[9]

West Nile Virus in the United States

In the United States during 1999 to 2000, 78 cases of West Nile meningoencephalitis were detected, all within the greater New York City metropolitan area, with most onsets in August and September. During August 1999, 5 patients with fever, confusion, and weakness were admitted to intensive care unit of the same hospital in New York City. Ultimately, 4 of the 5 cases developed flaccid paralysis and required ventilatory support. Three patients with less severe cases presented shortly thereafter. These were documented as the first cases of West Nile virus infection in North America.[10] The main epicenters in 1999 to 2000 were the New York City boroughs of Queens (32 cases) and Staten Island (10 cases).[7] Based on reports to the Centers for Disease Control and Prevention's ArboNET surveillance system, among the 123 nonfatal cases detected in 1999 to 2001, the median age of patients was 65 years (range, 5–90 years), with 73 (59%) patients aged more than 60 years, and 77 (63%) patients were male.[7] Among the 18 (13%) fatal cases, the median age was 75 years (range, 44–90 years). Sixteen (89%) were aged more than 60 years, and 8 (44%) were male.[7] The youngest patient was aged 5 years.[11] In all 10 counties subsequently reporting human cases in 2000, a West Nile virus–infected bird (American crow, *Corvus brachyrhynchos*) was found an average of 44 days (range, 15–92 days) before the onset of illness in the first human case.[12]

Birds infected with West Nile virus that have been reported to ArboNET include American crows, hawks, blue jays, ruffed grouse, gulls, house sparrows, American robins, mourning doves, and falcons.[12] Mammals infected with the West Nile virus include horses, big brown bat, little brown bat, eastern chipmunk, eastern gray squirrel, and the domestic rabbit.[12]

VIROLOGY

West Nile virus is a single-stranded RNA virus belonging to the family Flaviviridae, genus flavivirus. This virus is a member of the Japanese encephalitis virus serocomplex that contains several viruses, such as the St. Louis encephalitis, Japanese encephalitis, Murray Valley encephalitis, and Kunjin virus.[2] West Nile virus is genetically divided into 2 lineages, of which only lineage 1 is associated with human disease. The outbreak in New York City was caused by lineage 1 virus that circulated in Israel from 1997 to 2000, thus suggesting viral importation into North America from the Middle East.[2] The virus circulates in natural transmission cycles involving *Culex* mosquito species (*C. pipiens* in Europe and *C. univittatus* in Africa) and birds, humans being the incidental hosts.[13] Interestingly, both birds and humans have died of West Nile virus infection only in the United States and Israel; the reason for this is unknown.[2] Complete genome sequencing of a flavivirus isolated from the brain of dead Chilean flamingo (*Phoenicopterus chilensis*), together with partial sequence analysis of envelope glycoprotein (E glycoprotein) amplified from several other species including mosquitoes and 2 fatal human cases in 1999 New York epidemic, revealed that West Nile virus circulates in natural transmission cycles and was responsible for human disease.[14]

Table 1. West Nile Virus Cases in Humans from 1999 to 2003 in the United States

Year*	Number of States	Number of Cases	Number of Deaths
1999	1	62	7
2000	3	21	2
2001	10	66	9
2002	40	4156	284
2003	46	9858	264

*Data for years 1999 to 2001 from Asnis DS. West Nile virus infection in the United States: a review and update. Infect Med 2002;19: 266–78. Case counts for the year 2002 as of April 15, 2003 and for the year 2003 as of March 31, 2004. Data from Division of Vector-Borne Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention. West Nile virus statistics, surveillance, and control. Available at www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount03_detailed.htm. Accessed 05 Apr 2004. Last update 31 Mar 2004.

Transmission

West Nile virus infection in humans occurs through the bite of an infected culicine mosquito. Mosquitoes become infected by feeding on infected birds that have high levels of West Nile viremia. These infected mosquitoes then feed on humans (and other mammals) and infect them. Humans, horses, and most other mammals do not develop high-level viremia, do not transmit the virus through mosquito bites, and were therefore traditionally thought of as "dead-end" hosts.[15] In 2002,

Table 2. Symptoms and Signs of West Nile Encephalitis

Symptoms	Signs
Fever	Altered mental status
Headache	Weakness
Nausea	Tremor
Neck pain	Nuchal rigidity
Vomiting	Muscular rigidity
Myalgia	Bradykinesia
Chills/rigor	Postural instability
	Myoclonus
	Dysphagia

Adapted from Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection [published erratum appears in JAMA 2003;290:1318]. JAMA 2003;290:511–5.

however, new modes of transmission were recognized. Transmission of West Nile virus has been reported through organ transplantation,[16,17] blood transfusion,[16,18] breast-feeding,[19] transplacental transmission,[20] and by occupational exposure in laboratory workers.[21]

CLINICAL MANIFESTATIONS

The incubation period of West Nile viral infection ranges from 2 to 14 days. The frequency and severity of West Nile virus infection increases with age. West Nile viral infection can be asymptomatic or can manifest as West Nile fever, meningitis, encephalitis, and acute flaccid paralysis. Most people infected with West Nile virus are asymptomatic. Approximately 1 in 150 infected persons will develop severe illness with central nervous system (CNS) involvement.[2] Persons older than 50 years have a higher risk for developing neurologic consequences.

Patients with West Nile encephalitis present with behavioral or personality changes (manifested as irritability, confusion, or disorientation), fever, headache, body aches, neck pain, nausea, and vomiting. There may be associated chills and/or rigors. Neurologic findings on physical examination include depressed or altered level of consciousness, lethargy or personality changes, nuchal rigidity, tremors, myoclonus, and features of parkinsonism.[22] Uncommon neurologic features include cranial nerve abnormalities, myelitis, polyradiculitis, optic neuritis, and seizures.[2] The common symptoms and signs of West Nile encephalitis are shown in **Table 2**.

Encephalitis with severe muscle weakness and change in the level of consciousness are prominent risk factors predicting death.[2] Involvement of the CNS is associated with mortality of up to 10% and with long-term morbidity.[15]

Table 3. US National Case Definitions: Confirmed Cases of West Nile Encephalitis

Febrile illness with neurologic manifestations (headache, aseptic meningitis, myelitis, encephalitis) plus at least 1 of the following:

- Isolation of West Nile virus from tissue, blood, CSF, or other body fluids
- Demonstration of West Nile viral antigen or genomic sequence in tissue, blood, CSF, or other body fluids
- Demonstration of West Nile IgM antibody in acute CSF sample using MAC-ELISA
- Demonstration of 4-fold change in PRNT antibody titer to West Nile virus in paired, appropriately timed acute and convalescent serum samples
- Demonstration of both West Nile virus–specific IgM (by MAC-ELISA) and IgG (by ELISA or HI antibody titer; confirmed by PRNT) in a single serum sample

Adapted with permission from Peterson LR, Marfin AA. West Nile virus: a primer for the clinician. Ann Intern Med 2002;137:177.

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; HI = hemagglutination inhibition; MAC-ELISA = IgM antibody-capture enzyme-linked immunosorbent assay; PRNT = plaque reduction neutralization test.

DIAGNOSIS

West Nile encephalitis recently has been added to the list of nationally notifiable arboviral encephalitis. The criteria for a confirmed case of West Nile encephalitis are outlined in **Table 3**.

Differential Diagnosis

Certain clues raise the index of suspicion for a diagnosis of West Nile encephalitis (**Table 4**). The differential diagnosis of West Nile encephalitis varies depending on the severity of the presenting illness (ie, aseptic meningitis to encephalitis). Most cases of aseptic meningitis during the West Nile virus season (ie, summer and early fall) are caused by enteroviruses. Other pathogens with the more severe presentation of encephalitis include adenovirus, mumps, lymphocytic choriomeningitis viruses, Epstein-Barr virus, rabies virus, cytomegalovirus, HIV, and postinfectious encephalitides. Various systemic diseases, such as CNS vasculitis, sarcoidosis, and systemic lupus erythematosus, can mimic West Nile encephalitis. Among the arboviruses, the differential diagnosis includes St. Louis virus, Western and Eastern Equine virus, and La Crosse virus. St. Louis virus, Western Equine virus, and Eastern Equine virus affect all ages equally. The La Crosse encephalitis occurs primarily in children younger than

15 years (boys are more often affected than girls), whereas the West Nile encephalitis has a preponderance for people older than 50 years. Cross-reacting IgM antibodies may be detected in persons recently vaccinated against yellow fever or Japanese B encephalitis virus or those infected with dengue or St. Louis virus. West Nile virus IgM antibodies may remain positive for a year or more after infection, making this finding less useful in endemic settings.[23]

Diagnostic Testing

The most efficient diagnostic method is detection of IgM antibody to West Nile virus in serum or cerebrospinal fluid (CSF). The IgM antibody capture enzyme-linked immunosorbent assay (ELISA) is the optimal test for IgM detection because it is simple, sensitive, and applicable to samples of both serum and CSF. Because IgM does not cross the blood-brain barrier, IgM antibody in CSF strongly suggests CNS infection.[2] IgM antibodies can be detected in serum or CSF during the first 4 days of illness, and nearly all tests are positive by 7 to 8 days after onset of illness. IgM antibodies in the serum and CSF may persist for a year or more after infection.[23]

The plaque reduction neutralization test is the most specific test for arthropod-borne flaviviruses and can be used to distinguish false-positive results from other assays. Because ELISA and hemagglutination inhibition tests can cross react between West Nile, St. Louis encephalitis, yellow fever, dengue, and Powassan viruses, patients who test positive for antibodies to these viruses should be tested for specific neutralizing antibody.[24]

Serologic testing using the PCR method was used to analyze the seropositive confirmed cases of West Nile virus in the 1999 New York City outbreak. Five of the serologically confirmed cases and none of the controls were positive for West Nile virus. As antiviral research identifies drugs with activity against West Nile virus, the PCR technique is a useful tool.[25]

In identifying CNS inflammation, magnetic resonance imaging is more helpful than computed tomography scanning. A computed tomography scan in patients with West Nile virus encephalitis shows normal findings or preexisting lesions and long-term changes. In 30% of patients, magnetic resonance images show leptomeningeal or periventricular enhancement. High-intensity signal on T2-weighted images in the thalamus and basal ganglia may be an indicator that the patient has West Nile virus encephalitis.[15] CSF study in patients with West Nile encephalitis shows mild pleocytosis with lymphocytic predominance, increased protein, and normal glucose.[15]

Table 4. Clues to West Nile Encephalitis

Unexplained bird deaths in region
Mosquito season
Age more than 50 years
Muscle weakness and/or flaccid paralysis
Hyporeflexia
Electromyogram or nerve conduction velocity study showing axonal neuropathy
Lymphocytopenia
Magnetic resonance image showing enhancement of leptomeninges and/or periventricular area

Adapted with permission from Asnis DS. West Nile virus infection in the United States: a review and update. Infect Med 2002;19:266–78.

Pathologic findings at autopsy of 4 patients from New York City who died, as well as immunohistologic analysis of cortical tissue, showed only minimal evidence of viral inflammation in brain tissue.[26] Evidence of West Nile virus infection was more likely to be found in the brain stem than in other sites in the brain and extraneural tissue. In the most severe cases, there was evidence of scattered microglial nodules. Perivascular and perineuronal inflammation, primarily confined to the medulla and the cranial nerve roots, also were present. One patient was found to have hemorrhagic pancreatitis.[23]

TREATMENT

There is no specific treatment for West Nile virus infection. Antipyretics and analgesics may help in symptomatic treatment. Management is mostly supportive. No controlled studies have assessed the efficacy of ribavirin, interferon alfa-2b, corticosteroids, antiseizure medications, or osmotic agents in the management of West Nile encephalitis.

PREVENTION

The two main strategies for prevention of West Nile encephalitis are (1) reducing contact between humans and mosquitoes by using various personal protection, and (2) reducing the number of vector mosquitoes through actions taken by the local government authorities and by the public. Vaccines for West Nile virus are under development, but they most likely will not be available in the near future.

CONCLUSION

West Nile virus will continue to spread into the contiguous western United States over the next few years, mainly via the movement of viremic birds.[7] In summer

and fall of 1975, roughly 2000 cases of St. Louis encephalitis virus were documented, mainly in urban and suburban areas of central and southern United States. After many years and even decades, West Nile virus is likely to achieve an ecologic and epidemiologic equilibrium resembling that of St. Louis encephalitis virus.[7] Within the expanding ecology of West Nile virus, it is likely that additional large urban *C. pipiens* complex–driven West Nile encephalitis epidemics will occur in the near future. Cities with poor economic and sanitary infrastructure and those that lack West Nile virus surveillance are at greater risk. As West Nile virus becomes established in the United States, physicians, veterinarians, laboratory workers, and public health officials must remain vigilant for unexpected outbreaks of imported diseases. Physicians should have a high index of suspicion for West Nile virus infection when faced with a patient with the relevant neurologic manifestations during mosquito season. Additional information on the West Nile virus is available at www.cdc.ncidod/westnile/index.htm. **HP**

REFERENCES

1. Pile J. West Nile fever: here to stay and spreading. Cleve Clin J Med 2001;68:553–60.
2. Peterson LR, Marfin AA. West Nile virus: a primer for the clinician. Ann Intern Med 2002;137:173–9.
3. Tyler KL. West Nile virus encephalitis in America [editorial]. N Engl J Med 2001;344:1858–9.
4. Jia XY, Briese T, Jordan I, et al. Genetic analysis of West Nile New York 1999 encepahlitis virus. Lancet 1999;354: 1971–2.
5. Smithburn KC, Hughes TP, Burke AW, Paul JH. A neurotropic virus isolated from the blood of a native of Uganda. Am J Trop Med 1940;20:471–92.
6. Division of Vector-Borne Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention. West Nile virus statistics, surveillance, and control. Available at www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount03_detailed.htm. Accessed 5 Apr 2004. Last update 31 Mar 2004.
7. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. West Nile virus. Lancet Infect Dis 2002;2:519–29.
8. Tsai TF, Popovici F, Cernescu C, et al. West Nile encephalitis epidemic in southeastern Romania. Lancet 1998; 352:767–71.
9. Hubalek Z, Halouzka J. West Nile fever—a reemerging mosquito-borne viral disease in Europe. Emerg Infect Dis 1999;5:643–50.
10. Asnis DS, Conetta R, Teixeira AA, et al. The West Nile virus outbreak of 1999 in New York: the Flushing Hospital experience [published erratum appears in Clin Infect Dis 2000;30:841]. Clin Infect Dis 2000;30:413–8.
11. Update: West Nile virus activity—Northeastern United States, 2000. MMWR Morb Mortal Wkly Rep 2000;49: 820–2.
12. Marfin AA, Petersen LR, Eidson M, et al. Widespread West Nile virus activity, eastern United States, 2000. Emerg Infect Dis 2001;7:730–5.
13. Lanciotti RS, Kerst AJ, Nasci RS, et al. Rapid detection of West Nile virus from human clinical specimens, field-collected mosquitoes, and avian samples by a TaqMan reverse transcriptase-PCR assay. J Clin Microbiol 2000; 38:4066–71.
14. Lanciotti RS, Roehrig JT, Deubel V, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. Science 1999;286: 2333–7.
15. Sampathkumar P. West Nile virus: epidemiology, clinical presentation, diagnosis, and prevention. Mayo Clinic Proc 2003;78:1137–43.
16. Update: investigations of West Nile virus infections in recipients of organ transplantation and blood transfusion—Michigan, 2002. MMWR Morb Mortal Wkly Rep 2002;51: 879.
17. Iwamoto M, Jernigan DB, Gausch A, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med 2003;348:2196–203.
18. Investigations of West Nile virus infections in recipients of blood transfusions. MMWR Morb Mortal Wkly Rep 2002;51:973–4.
19. Intrauterine West Nile virus infection–New York, 2002. MMWR Morb Mortal Wkly Rep 2002;51:1135–6.
20. Possible West Nile virus transmission to an infant through breast-feeding–Michigan, 2002. MMWR Morb Mortal Wkly Rep 2002;51:877–8.
21. Laboratory-acquired West Nile virus infections–United States, 2002. MMWR Morb Mortal Wkly Rep 2002;51: 1133–5.
22. Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection [published erratum appears in JAMA 2003;290:1318]. JAMA 2003;290:511–5.
23. Petersen LR, Roehrig JT, Hughes JM. West Nile virus encephalitis. N Engl J Med 2002;347:1225–6.
24. Human West Nile virus surveillance—Connecticut, New Jersey, and New York, 2000. MMWR Morb Mortal Wkly Rep 2001;50:265–8.
25. Briese T, Glass WG, Lipkin WI. Detection of West Nile virus sequences in cerebrospinal fluid [letter]. Lancet 2000;355:1614–5.
26. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med 2001;344:1807–14.