Editorials

West Nile Virus Encephalitis in America

MOLECULAR diagnostic techniques, including the amplification of viral nucleic acid from cerebrospinal fluid by the polymerase chain reaction (PCR), have revolutionized the diagnosis of viral infections of the central nervous system.[1] Nevertheless, the causes of about two thirds of cases of presumed viral encephalitis remain unknown. In the United States, most cases of acute encephalitis are caused by herpes simplex virus (HSV), enteroviruses, and arthropod-borne viruses (arboviruses). Only arboviruses produce epidemics of viral encephalitis. Arboviruses represent a functional rather than a taxonomic group, linked by the importance of mosquito and tick vectors in their transmission, and their epidemiologic features, including seasonal incidence and geographic distribution, are constrained by the ecology of their transmitting vectors. The arboviruses that cause encephalitis in the United States include the St. Louis, California, western equine, and eastern equine encephalitis viruses.

The discovery that a cluster of cases of encephalitis in the New York City area in the summer of 1999 was caused by West Nile virus[2,3] was a masterstroke of medical detection, combining features of a Berton Roueché story, a Michael Crichton novel, and Alfred Hitchcock's *The Birds.* This arbovirus had not previously been isolated in North America, and the St. Louis encephalitis virus was originally suspected. Fifty-nine patients with West Nile virus infection who were hospitalized, including seven who died, are the subjects of the report by Nash et al. in this issue of the *Journal.*[4] Last year, 21 additional patients were given a diagnosis of West Nile virus infection in New York (14), New Jersey (6), and Connecticut (1). West Nile virus has been isolated from mosquitoes, more than 4000 birds, 58 horses, and a few small mammals (bats, rodents, rabbits, cats, raccoons, and a skunk) from an ever-widening geographic range. These findings strongly suggest that West Nile virus will continue to cause meningoencephalitis in North America, particularly in states along the Atlantic seaboard.[5-7]

West Nile virus was initially isolated in 1937 from the blood of a woman with a febrile illness in the West Nile district of Uganda. The virus is taxonomically related to other encephalitis-causing flaviviruses belonging to the Japanese encephalitis serogroup. West Nile virus is one of the world's most widely distributed arboviruses; it caused major outbreaks of meningoencephalitis in Romania in 1996 and in Russia in 1999. Analysis[3,8] of the nucleotide sequence of the West Nile virus envelope glycoprotein gene in several isolates from humans, mosquitoes, and birds from New York indicated that these viruses were at least 99.8 percent identical; they differed in only 2 of 1278 nucleotides from the sequence of a West Nile virus isolated in 1998 from the brain of a dead goose in Israel.[3] These results provided strong evidence that the West Nile virus responsible for infecting humans was circulating in a natural transmission cycle involving mosquitoes and birds. The remarkable degree of phylogenetic relatedness between the virus found in New York in 1999 and that found in Israel in 1998 suggests that the New York virus may have originated in the Middle East.[3,8]

Since West Nile virus can infect humans, birds, and mosquitoes, any of these hosts may have served as a vector for the introduction of the disease into the United States. The initial outbreak in humans coincided with the deaths from West Nile virus of several thousand American crows (*Corvus brachyrhyncos*) and the deaths of exotic birds in the Bronx and Queens zoos. This suggests that the virus was originally introduced into the United States by an infected migratory or imported bird[9] and that the infection was subsequently spread to other susceptible birds and to humans by ornithophilic mosquitoes (e.g., *Culex pipiens*). Humans are typically dead-end hosts for arboviruses, making it unlikely that an infected person traveling from an area where the virus is endemic was the initial source of infection. It is unlikely, but not impossible, that the virus was introduced into the country by infected mosquitoes or larvae arriving by ship or plane from an area where the infection is endemic.

Nash and colleagues describe the basic clinical, epidemiologic, diagnostic, and laboratory features of the 59 patients with West Nile virus meningoencephalitis who were hospitalized in the New York City area during the 1999 epidemic.[4] These patients accounted for 27 percent of the patients with encephalitis and muscle weakness, 14 percent of those with encephalitis alone, and 6 percent of those with aseptic meningitis whose cases were reported in New York City during this time. It is likely that there were 150 or more undiagnosed asymptomatic or mildly symptomatic persons for each recognized case of severe neurologic illness.[10] Diagnosis was based primarily on the detection of IgM antibodies against West Nile virus in cerebrospinal fluid (30 cases) or, when cerebrospinal fluid was negative or not available, by the presence in serum of both IgM antibodies against West Nile virus and neutralizing antibodies (29 cases). As in previous studies, West Nile virus was never cultured from cerebrospinal fluid or brain tissue.

A total of 57 percent of the cerebrospinal fluid specimens tested by PCR were positive for West Nile virus RNA. In HSV encephalitis, the amount of HSV DNA detected in cerebrospinal fluid by PCR declines rapidly after the first two weeks of infection,[11] whereas the intrathecal synthesis of antibodies against HSV increases after the first week. Nash et al.[4] do not provide information on the timing of the PCR testing of cerebrospinal fluid or of the antibody studies. Sensitive, specific, and early diagnosis of West Nile virus infection is crucial for the implementation of appropriate public health measures to limit or prevent outbreaks of disease.

Physicians, like poker players, are always searching for an opponent's characteristic quirks that may provide a clue to the nature of his or her hand. West Nile virus offers several potential clues that should alert physicians to the possibility of the disease. First, unexpected deaths in bird or horse populations are likely to be sentinel events that precede the infection of humans. Second, although West Nile virus infects persons of all ages, the risk of meningoencephalitis increases by a factor of more than 20 in those older than 50 years of age.[4]

Third, West Nile virus has some clinical features, including the pattern of weakness and the presence of neuropathy, that are unusual in other forms of encephalitis: 27 percent of the patients in the study by Nash et al. had muscle weakness, 32 percent had diminished reflexes, and 10 percent had diffuse flaccid paralysis, in some cases resembling Guillain–Barré syndrome. Electromyelography and nerve conduction studies indicated an axonal neuropathy in those with flaccid paralysis, although there were also features consistent with demyelination. Unlike patients with classic Guillain-Barré syndrome, all those hospitalized with West Nile virus infections had pleocytosis. The low incidence of seizures (3 percent) and the high incidence of abnormal cranial-nerve function (22 percent) may reflect the predilection of West Nile virus for the brain stem.

Finally, a significant proportion of patients (19 percent) had an erythematous rash, and many had lymphocytopenia, both relatively unusual features in viral encephalitis. The presence of any of these features should raise suspicion of West Nile virus and prompt definitive diagnostic testing.

Neuroimaging studies are routinely performed in patients with suspected meningoencephalitis, although few studies have correlated abnormalities found on neuroimaging with specific viral infections. Although the findings are not described in detail, magnetic resonance imaging (MRI) showed an abnormal "enhancement of the leptomeninges, the periventricular areas, or both" in 31 percent of the patients with West Nile virus.[4] By contrast, 94 percent of patients with HSV encephalitis, the most common type of severe acute, sporadic encephalitis in the United States, have focal areas of increased T_2-weighted signal in the temporal lobes on MRI.[12]

There are several critical lessons to be learned from the West Nile virus epidemic. First, clinicians must remain alert for clusters of unusual cases of illness. Investigation into the West Nile virus outbreak was initially triggered by the astute observations of a specialist in infectious diseases who contacted the New York City Department of Health.[13] Second, physicians must press vigorously for autopsy evaluations of patients who die of unexplained or unusual illnesses. Autopsy studies helped confirm the cause and nature of the West Nile virus cases.[14] Third, "new" viral infections frequently result from changes in the host range, geographic distribution, or ecology of previously known pathogens. Physicians must remain alert for new outbreaks of disease in animals, which may herald related events in humans. Finally, the rapid and dramatic success in identifying, understanding, and controlling the West Nile virus epidemic in the United States is a tribute to the coordinated efforts and contributions of local and national public health organizations and a dedicated group of physicians and scientists.

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