CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

West Nile fever: Lessons from the 2002 season

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ABSTRACT

West Nile fever has now spread to much of the United States. This disease can be diagnosed using one of several laboratory tests, notably an immunoglobulin M enzyme-linked immunosorbent assay. It can cause devastating neurologic damage, including an unusual polio-like syndrome. Magnetic resonance imaging is an important imaging tool in such patients. Treatment is largely supportive, although antiviral agents are under investigation.

LAST YEAR WE LEARNED many things about West Nile fever, yet we still have many questions. Among the lessons learned:

- The immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) is the most practical test for West Nile virus
- Age greater than 50 years appears to increase the risk of neurologic consequences
- West Nile fever can cause a polio-like syndrome, with severe muscle weakness
- West Nile fever can cause encephalitis with concomitant myelitis; therefore, magnetic resonance imaging (MRI) should be obtained of the brain and spinal cord
- Mollaret-type cells in cytologic review of the cerebrospinal fluid may prove to have high predictive value
- In cases of meningoencephalitis that occur in the summer, clinicians should consider treatable infections and syndromes including other viruses (eg, herpes simplex virus or enterovirus) or neurologic syndromes that may masquerade as viral infection (eg, Guillain-Barré syndrome)
- West Nile encephalitis or meningitis cannot be clinically distinguished from other viral infections of the central nervous system; therefore, specific diagnostic testing should be sought
- Blood transfusions pose a small (perhaps 1 in 10,000) but real risk of transmitting West Nile virus.

Despite all we have learned about West Nile fever, the key issue of how best to treat the serious manifestations of this disease remains unknown.

In this article we use a case discussion to outline some of the things we learned in the 2002 outbreak in Northeast Ohio, and what we have yet to learn.

PATIENT INFORMATION
Reducing your risk of West Nile virus, page 455

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion. Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

A 40-YEAR-OLD MAN WITH FEVER, NAUSEA, AND VOMITING

The index case of West Nile virus infection in Cleveland was in a 40-year-old man who was hospitalized August 2, 2002, after experiencing fever, chills, nausea, and vomiting for 3 days.

The patient had a normal computed tomography (CT) scan of the head and a normal chest radiograph. His white blood cell count was 11.8 × 10^3/μL (normal 4.0–11.0). Fever continued, and a lumbar puncture on August 4 showed a white blood cell count of 220/μL (normal 0–5) with a polymorphonuclear predominance.

West Nile fever closely resembles St Louis encephalitis

West Nile virus 2002: The Cleveland Clinic experience

Twenty-three patients were hospitalized with West Nile virus infection at The Cleveland Clinic in 2002. Of these:

- The mean age was 64 years (range 12–85)
- 4 (17) were younger than 50 years
- 3 (13%) died
- 6 (26%) presented with a rash
- All patients had meningitis or meningoencephalitis (1 patient had rhomboencephalitis)
- Significant weakness developed in 11 patients (48%) and evolved to flaccid paralysis in 9 patients (39%)
- 1 case was associated with transfusion.

Antibiotics and acyclovir were given as empiric measures. Nevertheless, the patient's condition deteriorated until he required intubation, with progressive flaccid weakness in his limbs, bilateral facial plegia, and severe bilateral weakness of the orbicularis oculi muscles. Eventually, he appeared to have a "locked-in" syndrome: although he had almost no movement in three of his four limbs, he seemed aware and could respond to commands by blinking his eyes, sticking out his tongue, and giving the "thumbs up" sign.

West Nile virus has an incubation period of 3 to 14 days

HOW WEST NILE FEVER PRESENTS

West Nile virus, an RNA virus, is a member of the flavivirus family, which includes the viruses responsible for dengue fever and hepatitis C.[1] Specifically, it belongs to the Japanese encephalitis complex, which also includes the agents of St. Louis encephalitis and Murray Valley encephalitis.

It has an incubation period of 3 to 14 days. Of persons infected, 20% experience a febrile illness, and 1 in 200 develop neurologic disease, almost all of whom are hospitalized. Signs and sequelae in those hospitalized:

- Fever: more than 90%
- Weakness: 50%
- Headache: more than 50%
- Mental status changes: 34% to 50%
- Rash: 20%
- Diarrhea: 27%
- Death: 5% to 10%.

Persons over age 50 appear to be at greatest risk of neurologic consequences. Before the first frost of the fall, several clinical patterns should prompt consideration of West Nile fever, including:

- Viral encephalitis with concomitant myelitis
- Guillain-Barré syndrome
- Aseptic meningitis
- Viral meningoencephalitis, and rhomboencephalitis.

ACUTE FLACCID PARALYSIS OR POLIO-LIKE SYNDROME

West Nile fever can sometimes present with a very unusual, polio-like variant. It can cause severe muscle weakness (inability to walk) often with axonal neuropathy and requiring mechanical ventilation, but unlike Guillain-Barré syndrome, the weakness is distal more than proximal, and there is no pleocytosis in the cerebrospinal fluid in Guillain-Barré syndrome.

Examination of the spinal cord of one patient found anterior horn cell damage, usually characteristic of polio.

West Nile fever can cause encephalitis with concomitant myelitis; therefore, MRI of the brain and spinal cord should be performed.[2]

CASE CONTINUED

Because of this patient's serious neurologic symptoms, MRI of the brain and spinal cord was ordered. It showed patchy areas of increased signal on the flair image and on the T2-weighted images in the pons with extension to the brachium pontis. Rhomboencephalitis

was diagnosed, a condition usually equated with *Listeria* infection. MRI of his spine showed extensive conus lesions, as well as smaller lesions in the cervical cord (FIGURE 1).

The diagnosis of probable acute West Nile virus infection was suggested by the presence of IgM in both cerebrospinal fluid and serum (by capture ELISA) and was confirmed by the plaque reduction neutralization test (performed at the Center for Arbovirus and Vectorborne Diseases, Centers for Disease Control and Prevention (CDC), Fort Collins, Col).

DIAGNOSTIC TESTING

West Nile encephalitis or meningitis cannot be clinically distinguished from other viral infections of the central nervous system; therefore, specific diagnostic testing should be sought. During mosquito season, cerebrospinal fluid and serum should be obtained from patients hospitalized with any illness suggestive of the disease and sent for arboviral encephalitis screening that includes West Nile virus. Routine testing is not recommended, however, for mild febrile illness, even with a history of a mosquito bite.

Serologic tests: IgM ELISA is most practical

ELISAs are available for West Nile IgM and IgG antibodies, although they were not readily accessible last summer. The tests are now commercially available from Focus Technologies (Herndon, Va), and great efforts are being made to have them distributed to hospital laboratories for the upcoming 2003 season.

The IgM ELISA is the most practical test for West Nile virus. It can be done in any setting, takes only a few hours, and has good sensitivity for acute disease, although its specificity is less clear. IgM antibodies may be present as early as the first day of illness and are always present in the cerebrospinal fluid by the time meningoencephalitis has manifested.

The IgG ELISA for West Nile virus is less specific because it cross-reacts with other flaviviruses.[3]

The real-time polymerase chain reaction test can detect West Nile virus in mosquito

West Nile fever: Rhomboencephalitis, myelitis

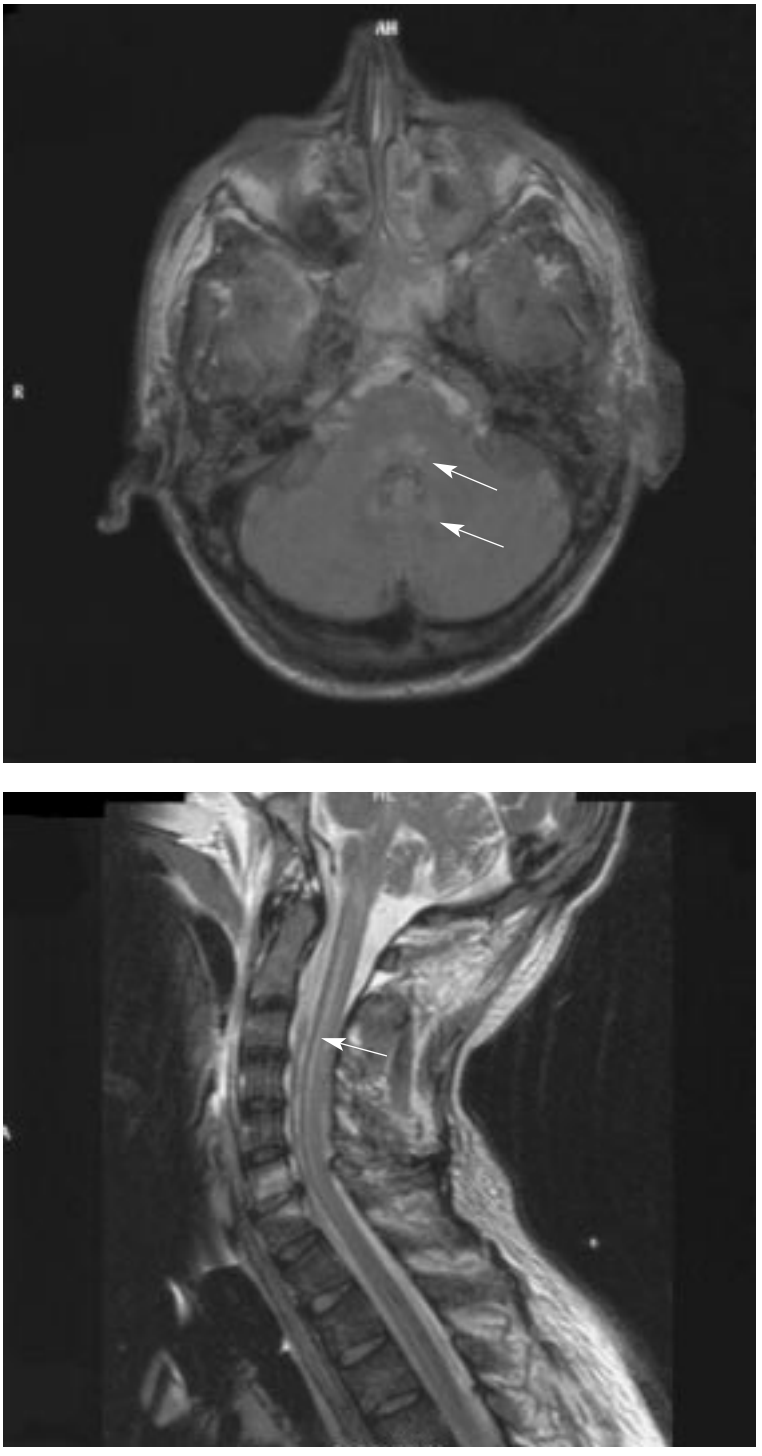

FIGURE 1. Top, MRI of the brain of a patient with West Nile fever, showing rhomboencephalitis (arrows). **Bottom,** MRI of the spinal cord showing increased signal intensity (arrow), indicating myelitis.

A history of an outbreak

West Nile virus, which was first isolated in 1937 from the blood of a Ugandan woman, is widely distributed throughout Africa, the Middle East, parts of Europe, and Asia. The most recent outbreaks outside the United States were in Romania in 1996 and Israel in 2000.

The virus slipped into the United States in 1999, perhaps in an infected person or mosquito, but more likely in an infected exotic bird smuggled into the country.

One US Senator suggested that the West Nile fever outbreak might represent a bioterrorist attack. That is very unlikely, given the epidemiology of the outbreak and the molecular typing of the strain.

The disease first became noticed after an unusual number of deaths of exotic birds at the Bronx Zoo in New York City. The avian casualties were soon linked to a human outbreak in the New York City borough of Queens. Sixty-two persons tested positive for West Nile virus; 7 of them died. A serologic survey of Queens residents indicated that 2.6% were infected with the virus.

Hope that the mosquitoes responsible for the outbreak would die when the weather turned cold quickly dissolved when mosquitoes found in the city's sewer system the following winter tested positive for the virus. Each succeeding summer, the disease has spread westward—literally as the crow flies. During 2002, a total of 3,052 human cases with laboratory evidence of West Nile virus infection were reported, including 153 deaths.

A VIRUS OF BIRDS AND MOSQUITOS

West Nile fever originally was misclassified in the United States as St. Louis encephalitis, which it closely resembles in range and clinical presentation. These two diseases also share a vector, the night-biting *Culex pipiens* mosquito, which can be recognized by the "airplane" position it takes when resting on the skin.

The virus typically is transmitted from mosquito to bird and back to mosquito. Dozens of species of North American birds have tested positive. Crows are the most conspicuous victims because they die en masse, but the ubiquitous house sparrow probably is the most important reservoir. Unlike malaria, West Nile virus is not transmitted from human to human through mosquitoes.

The strain of West Nile virus responsible for the North American human outbreak was found to be closely related to an Israeli duck isolate, although the exact source has never been pinpointed. Regardless, West Nile virus became the fifth type of clinically significant arthropod-borne virus (arbovirus) identified in North America, along with Western equine encephalitis, Eastern equine encephalitis, LaCrosse encephalitis, and St. Louis encephalitis.

pools and human tissue, but is not very sensitive in cerebrospinal fluid.[4]

Viral isolation grows and produces a cytopathic effect or plaques in a variety of cell lines (human, primate, and mosquito). West Nile virus can be isolated from the blood in 77% of cases on the first day of illness, but patients remain viremic less than 5 days.

Plaque reduction neutralization is the most specific of the serologic tests, but it uses live viruses and therefore is done only at the CDC laboratory in Ft. Collins. It is considered the confirmatory test.

In outbreaks of new diseases, we cannot count on public health laboratories for support in managing clinical cases. This realization should galvanize development of in-house assays to support treatment protocols and research.

Guidelines from the CDC[5] state that a positive IgM ELISA in serum along with a clinical scenario suggestive of West Nile fever is enough for the diagnosis of "probable" acute or recent West Nile virus infection. Definite diagnosis requires viral isolation, cerebrospinal fluid positive for IgM by ELISA, or a fourfold or greater increase in antibodies by plaque reduction neutralization testing performed on sera from the acute and convalescent stages of illness.

Paired sera should be drawn at least 2 weeks apart. Samples should be sent to the appropriate state health laboratory, which

may in turn send the samples to the CDC for confirmation.

Cerebrospinal fluid characteristics

The studies of the cerebrospinal fluid of the hospitalized patient with neurologic manifestations of West Nile virus infection were very interesting:

The mean protein concentration was 118 mg/dL (normal range 15–45 mg/dL) However, the range could vary, with results in different patients from 38 to 317 mg/dL.

The mean white cell count was 139/µL (normal range 0–5). However, we had some patients in whom the white blood cell count was very high: one had almost 1,500/µL, and many had a predominance of polymorphonuclear cells. This contradicts what many of us learned in medical school, that polymorphonuclear cell counts are low (100 to 200/µL) in viral infections.

Mollaret-like cells. One of the most surprising findings was that Mollaret cells were seen in 3 of 4 patients who underwent cytologic testing. Mollaret cells, which have a monocyte macrophage origin, are unique to Mollaret meningitis and are thought to be associated with herpes simplex virus. This is the first time such a finding had been reported; the presence of these cells may provide an early clinical clue that meningitis or encephalitis is due to West Nile virus, while awaiting serologic testing.

Imaging studies: MRI is more accurate than CT

West Nile fever can cause encephalitis with concomitant myelitis; therefore, MRI of the brain and spinal cord should be obtained when there is clinical evidence of encephalitis and myelitis or other spinal cord involvement.

MRI is considered more accurate than CT because it shows signal intensity within the cauda equina of the spinal cord. Although no finding is considered pathognomonic for West Nile fever, the brain stem and the medulla seem to be involved disproportionately.[6]

CASE CONTINUED

Once the diagnosis of West Nile fever was made in our patient, and given his devastating neurologic damage, he was given ribavirin, interferon alfa, and OmrIgam (an immune globulin preparation made in Israel, not available in the United States). OmrIgam was obtained through the US Food and Drug Administration and the Israeli pharmaceutical company that produces it. Although the patient showed no clinical improvement within the first 2 weeks, he eventually gained some strength in his legs, became more alert, and was able to press a call button. Unfortunately, he eventually had to be transferred to a long-term care facility.

TREATMENT: SUPPORTIVE CARE—NO OTHER PROVEN OPTIONS

We still know little about effective treatment of West Nile fever.

Current treatment is supportive. Symptomatic treatment in milder cases includes analgesics and antipyretics. More severe cases may require more aggressive care, including mechanical ventilation.

Investigational treatment options for West Nile fever are limited to agents tested in vitro—usually drugs that are effective against Flaviviridae. Ribavirin, interferon alfa, and OmrIgam have been used with little or no success.

Treatment options for West Nile fever are limited

Ribavirin. The use of ribavirin to treat West Nile virus has been rejected by most experts. The doses that inhibit the virus in vitro are so high (4 g/day—much higher than the dosage used to treat hepatitis C) that there is a serious risk of profound hemolytic anemia.

OmrIgam is an immunoglobulin preparation from Israel, where exposure to West Nile virus is relatively common, and thus the titer of West Nile IgG is fairly high.[7] In essence, it is used as West Nile immunoglobulin. We treated our patient with OmrIgam, with little effect.

Interferon alfa-2b has demonstrated anti-West Nile virus activity in vitro, but has not been studied in human disease in a controlled fashion.[8]

Corticosteroids. Given the short period of viremia in West Nile fever, there has been speculation that much of the neurologic damage results from the immune response to the virus. However, until we understand this virus

better, we are reluctant to give immunosuppressant medication.

PREVENTION

An engineered strain of West Nile virus vaccine using a weakened strain of yellow fever has proven protective in animal models.[9] It is to be tested in humans soon and may be available in 2003.

All people should be advised to use mosquito repellents containing diethyltoluamide (DEET) when they expect to spend time in areas known to harbor mosquitoes or when outdoors at night. They also should be advised to eliminate breeding sites, such as birdbaths, from their property (see "Reducing your risk of West Nile virus," page 455).

TRANSFUSION-ASSOCIATED CASES ARE RARE

Humans bitten by infected mosquitoes are "dead-end" hosts in that humans do not remain viremic for long and do not pass the disease on to other humans except in rare transfusion-associated cases.[10]

In the fall of 2002, West Nile fever was diagnosed in a 74-year-old woman who received a transfusion at The Cleveland Clinic. This case was transmitted perioperatively through a red blood cell transfusion from a donor with acute West Nile virus infection.[11]

The risk of transfusion-associated spread is probably less than 1 in 10,000, depending on disease activity in blood donor areas. Experts are currently investigating the possibility of routine screening for West Nile virus in donors, but this process may prove to be impractical because of time and cost factors. Screening for antibodies to West Nile virus is probably impractical. By the time antibodies appear, the individual is probably no longer viremic. Current efforts are directed at diagnostic testing using nucleic acid testing for West Nile virus screening of blood.

West Nile virus can be transmitted through breast milk, although the risk is unknown. In October 2002, a breast-feeding infant tested positive for West Nile virus after the mother was found to be infected. The infant was asymptomatic. However, because the benefits of breast-feeding are well known, mothers who are breast-feeding should continue to do so. No evidence suggests that West Nile virus can be transmitted from mother to fetus.

Acknowledgments: *We would like to thank the members of the Ad Hoc West Nile Virus Working Group at The Cleveland Clinic Foundation: Gary Procop, MD, Belinda R. Yen-Lieberman, PhD, and Geraldine S. Hall, PhD (Department of Clinical Pathology); Cathy A. Sila, MD, Richard Lederman, MD, PhD, and Michael DeGeorgia (Department of Neurology); Richard Prayson, MD, Paul M. Ruggieri, MD (Department of Radiology); and Cynthia Fatica, RN (Department of Infection Control and Epidemiology). Thanks also to all clinical staff and personnel, our patients, and their families.*

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