REVIEW ARTICLE

The West Nile Virus: A Lesson in Emerging Infections

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Since its identification in New York City in 1999, the West Nile virus has spread to 45 states and caused human infections in at least 44 states. West Nile virus is difficult to correctly diagnose without a high level of clinical suspicion and can cause severe debilitation or death in those with the most severe symptoms. This paper reviews the epidemiology, surveillance, prevention, clinical features, diagnosis, and treatment of this important emerging infection. Lessons learned from West Nile virus are discussed at the conclusion of the paper.

Key words: West Nile virus, mosquito, emerging infection

Introduction

In August 1999, the West Nile virus (WNV) caused an outbreak in New York City leaving 7 patients dead.¹ This was the first outbreak of WNV in the Western Hemisphere, and since this initial episode, the virus has spread to at least 45 states and infected humans in 44 states and the District of Columbia.^{2,3} This review discusses the epidemiology of WNV, its dissemination across the United States, and measures to prevent the infection and limit its spread.

Epidemiology

West Nile virus infections have been reported for many years in the Middle East and Asia. It was first isolated from a female patient in the West Nile district of Uganda.⁴ The first reported epidemic was in Israel in the 1950s. Since then, outbreaks have occurred in France, Russia, South Africa, Ukraine, Morocco, Romania, Tunisia, and Italy.⁴

The first recognized case of WNV in the Western Hemisphere occurred in New York City in 1999.¹ After this reported case, the virus quickly spread across the continental United States (Figure 1) and has caused infections in humans in 44 states. A total of 7386 human infections and 155 deaths were identified during the first 10 months of 2003.^{2,3} This rapid spread has caused alarm and has prompted the Centers for Disease Control

and Prevention (CDC) to pour \$35 million into combating dissemination of the virus.⁵

West Nile virus is an Arbovirus of the Flavivirus family and is similar to other arthropod-borne Flaviviruses that cause encephalitis, such as St Louis encephalitis, Japanese Polynesian virus, and Murray Valley virus.⁴ The virus is transmitted by female mosquitoes, usually the *Culex* species, and birds serve as amplifying hosts.⁶ Over 130 species of birds have been found to be infected with WNV, and of the approximately 200 species of mosquitoes in the United States, at least 36 carry the virus.⁷ West Nile virus can be broken into 2 genetic lineages, but only lineage 1 is associated with human infection.⁸ The virus that caused the New York City outbreak in 1999 was a lineage 1 virus similar to the virus that caused the outbreak in Israel a few years earlier.^{8,9} The first isolation of WNV from a patient in the Western Hemisphere with encephalitis occurred in September 2001.¹⁰

Surveillance

Although ascertaining accurate avian maintenance cycles of the virus is difficult, high mortality rates in birds do seem to correlate with human outbreaks.¹¹ Surveillance of dead birds, particularly crows, and other ill animals has been used to demonstrate the spread of the virus across the country^{12,13} and to target geographic regions for intervention. In Arkansas, a surveillance system that tested mosquitoes and dead wild birds for WNV identified the first occurrence of WNV in that state in 2001.¹⁴

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West Nile virus in humans in the United States.

A CDC workshop recommended these methods for surveillance of WNV:

1. Active bird surveillance
2. Active mosquito surveillance
3. Enhanced passive veterinary surveillance
4. Enhanced passive human surveillance¹⁵

A more sophisticated method of surveillance was also used in New York City and reported by Theophilides and colleagues.¹⁶ They described the use of Dynamic Continuous-Area Space-Time analysis to “identify and prospectively monitor high-risk areas for West Nile virus in New York, (New York City).”¹⁶ According to the authors, the Dynamic Continuous-Area Space-Time system is based on the following 4 assumptions:

1. West Nile virus is a continuous phenomenon across space
2. Humans are infected at their place of residence
3. Nonrandom space-time interaction of bird deaths is attributed to WNV infection
4. Each dead bird has an equal opportunity of being reported

By geocoding the location of each dead bird, the system was able to use a geographic information system to identify “areas of high risk for West Nile virus in humans at least 13 days prior to their onset of illness in 5 of the 7 human cases.”¹⁶

Nonvector Transmission

Concern has been raised about WNV being transmitted through blood transfusions. During 2002, a total of 42 WNV infections were thought to have been caused by blood transfusions.¹⁷ A study to determine the estimated risk of acquiring WNV through a blood transfusion in Queens, New York, during the WNV epidemic reported “a small but nonzero risk of WNV transmission from transfusion of blood components,”¹⁸ and a recent investigation quantifies the general risk as being between 1.46 and 12.33 per 10 000 donations.¹⁹

Transmission of WNV has been associated with red blood cells, fresh-frozen plasma, and platelets.²⁰ Trans-

mission through solid organ transplantation has also occurred.²¹ Although a national blood-donation screening program has been implemented and has been successful, WNV is still a concern because it occasionally occurs through donations from asymptomatic donors with small levels of viremia.²² Currently, WNV detection requires that the carrier have the antibodies to WNV. However, if the donor is newly infected with the virus, the antibodies may not be present at the time of donation. This conundrum caused the Food and Drug Administration to request companies to quickly develop nucleic acid tests to detect WNV genetic material before the peak mosquito season in 2003, calling it a “race against the mosquitoes.”¹⁷

In December 2002, the first in utero transmission of WNV was reported.²³ Although the child was born with significant neurological abnormalities, whether the WNV infection was the cause has not been determined. Other reports indicate that the virus is present in breast milk and transmissible to breast-fed infants.⁷ Lab workers who handle pathological samples containing WNV are also at risk for infection, and 2 cases of percutaneous inoculation were discussed in *Morbidity and Mortality Weekly Report*.²⁴

Clinical Features

Most humans infected with WNV remain clinically asymptomatic or silent, and there are approximately 150 asymptomatic cases for every severely symptomatic neurological case.²⁵ The CDC divides symptomatic cases into mild and severe.²⁶ Mild cases have a flulike illness typified by the sudden onset of fever, malaise, anorexia, nausea, headache, and occasionally a rash. Severe cases occur most frequently in patients of advanced age and present as fever with weakness that sometimes progresses to flaccid paralysis.²⁶

Recent studies regarding the neurologic manifestations of severe WNV have indicated that movement disorders seem to be a prominent finding in most patients with severe WNV encephalitis. In particular, parkinsonism, tremor, and myoclonus were found to be associated with WNV encephalitis, and these disorders have been found with other viral infections such as St Louis encephalitis and Japanese encephalitis but have not been associated with WNV until recently.²⁷ The mortality rate for WNV in hospitalized patients is estimated to be between 10% and 15%; patients with both encephalitis and weakness have a mortality rate of approximately 30%.²⁴

Diagnosis

Diagnosis of WNV is dependent upon high clinical suspicion. For any patient with encephalitis or meningitis

Table 1. Diagnostic studies for West Nile Virus²⁶

<i>Procedure</i>	<i>Result</i>
Total leukocyte count	Normal or increased with lymphocytopenia
Serum sodium	Hyponatremia
Cerebrospinal fluid	Pleocytosis with predominance of lymphocytes, increased protein, and normal glucose
Cerebral computerized tomography	Normal
Cerebral magnetic resonance imaging	Enhancement of leptomeninges or the periventricular areas

of unknown origin, WNV should be considered. For patients older than 50 years who present with encephalitis during the summer or early fall, WNV infection should be strongly considered.²⁵

Patients in whom WNV is suspected can have either serum or cerebrospinal fluid examined for immunoglobulin M antibodies to WNV.⁸ Because immunoglobulin M does not cross the blood-brain barrier, the presence of the immunoglobulin M antibody to WNV in cerebrospinal fluid “strongly suggests central nervous system infection.”²⁶ Patients with WNV infections should be reported to the local public health department.

Individuals recently infected with or vaccinated against similar viral illnesses such as yellow fever, Japanese encephalitis, or dengue can have false-positive reactions for WNV.²⁶ Table 1 lists additional laboratory and imaging results that could aid in the diagnosis of WNV.

Treatment and Clinical Outcome

The treatment for WNV is supportive. Ribavirin and interferon are both effective against WNV in vitro but have not proven to be effective in clinical trials.⁸ Other medications, such as steroids and osmotic agents, have not been subjected to controlled studies.⁸

Scant data exist concerning the long-term outcome of patients infected with WNV. Of those patients hospitalized during the year 2000 in New York and New Jersey, half did not regain their previous functional level.²⁸ This is significant long-term morbidity and highlights the importance of preventative measures against WNV.

Prevention

Means of prevention recommended by the CDC include vector control and mosquito bite reduction.⁵ Eliminating sources of mosquito larvae breeding sites, such as water in flowerpots, birdbaths, and swimming pool covers, is an important public health measure.

People living in areas where WNV is a concern

should be encouraged to use mosquito repellents.⁸ Two studies have compared the efficacy of various commercial types of mosquito repellent.^{29,30} In both investigations, repellents with N,N-diethyl-3-methylbenzamide (DEET) were superior for prevention of mosquito bites. DEET is applied directly to the skin, and repellents with DEET concentrations of at least 23.8% are highly effective in reducing mosquito bites for up to 5 hours.³⁰

Permethrin, an insecticide that kills mosquitoes so rapidly it can appear to be a mosquito repellent, is used to impregnate fabrics, such as bed nets³¹, tents^{32,33}, tarpaulins³⁴, and clothing^{35,36} and has reduced mosquito-borne disease transmission.^{31–37} The combination of DEET on the skin and permethrin on the clothes significantly reduces the frequency of mosquito bites better than either agent alone.^{38,39}

Allergic reactions to DEET-containing agents include bullous eruptions, contact urticaria, and anaphylaxis. Toxic encephalopathy, with grand mal seizures and even death, has rarely occurred in young children as a result of excessive exposure to DEET.^{8,29} The American Academy of Pediatrics recommends that repellents with more than 10% DEET not be used for children younger than 10 years of age and that DEET repellants not be used at all for children under the age of 2 months.⁸ Repellents such as Avon *Skin-So-Soft* or products containing citronella are much less effective in reducing mosquito bites.^{29,30}

Inventive strategies or products for mosquito control and bite prevention, such as small ultrasonic electronic devices or backyard bird or bat houses to encourage natural predation, have been unsuccessful.^{29,40} The popular bug zappers fail to prevent mosquito bites or kill mosquitoes because mosquitoes “continue to be more attracted to humans than to the devices.”²⁹ In one report on electronic bug zappers, less than 1% of the insects killed were female mosquitoes.⁴¹ An estimated 71 to 350 billion insects beneficial to human beings are killed every year in the United States by zappers.⁴¹

The United States Environmental Protection Agency has approved a handful of larvicides and adulticides to

Table 2. Larvicides and adulticides frequently used for mosquito control¹⁵

Larvicides	Adulticides
Temephos (Abate, BASF Corporation, Mount Olive, NJ), an organophosphate	Malathion, an organophosphate
<i>Bacillus thuringiensis israelensis</i> (Bti), a bacterial larvicide	Naled, an organophosphate
<i>Bacillus sphaericus</i> , a bacterial larvicide	Permethrin, a synthetic pyrethroid
Methoprene (Altosid, Wellmark International, Schaumburg, IL), an insect growth regulator	Resmethrin, a synthetic pyrethroid
Golden Bear, petroleum based oil	Sumithrin, a synthetic pyrethroid
Bonide, mineral based oil	Natural pyrethrins
Diffubenzuron (Dimilin, Crompton Corporation, Middlebury, CT), a chitin synthesis inhibitor	

help control mosquito populations. Whereas the larvicides are generally more effective in reducing mosquito numbers, the adulticides are still an “extremely important part of any integrated mosquito management program.”¹⁵ Table 2 lists common larvicides and adulticides.

During the New York City outbreak, public health officials sprayed high-risk areas with pesticides.⁴² Though pesticide spraying for mosquitoes results in few serious adverse health problems,⁸ the spraying in New York City created a firestorm of criticism from environmental groups and raised many ethical and legal questions about the use of pesticides to combat vector-borne diseases.⁴³

Another means of prevention being developed is a vaccine for humans. Currently, a vaccine for horses is available through veterinarians—the mortality rate for horses that develop WNV encephalitis is 40%—but human trials of a WNV vaccine are just beginning.⁷ The two most viable vaccine possibilities are, first, a chimeric vaccine developed by combining genetic material from the WNV and dengue viruses⁴⁴ and second, inoculation with the Kunjin virus, a Flavivirus similar to WNV but with minimal pathogenicity in humans.⁴⁵ Both vaccines have demonstrated favorable efficacy in animal models and should soon begin human testing.

Lessons for the Future

The WNV epidemic that began in New York City in 1999 holds many lessons for clinicians and those in public health. The virus was originally detected by a clinician who noted an unusually large cluster of new neurologic syndromes and contacted the local health department. It has since been argued by Crupi and colleagues⁴⁶ that this scenario is similar to what would occur after a terrorist attack with a biologic agent.

A high level of clinical suspicion and proper communication and collaboration with local public health authorities was developed and handled well during the WNV outbreak, but laboratory support and expert medical support were lacking.⁴⁶

The anthrax attack through the United States postal system⁴⁷ and the recent SARS epidemic⁴⁸ demonstrate that the lessons of the WNV epidemic must be mastered. Opportunities for mistakes will no doubt be present again. Effective measures for integrating the efforts of hospitals and public health departments must be pursued to diminish the impact of WNV and similar outbreaks.

Conclusion

WNV is a potentially debilitating disease that first presented in the Western Hemisphere in a 1999 New York City outbreak. Its rapid spread across the continental United States gave the virus the classification of an emerging infection, and efforts to control its impact still continue. The lessons from the detection and pursuit of this virus should be carefully considered by clinicians and public health officials.

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