West Nile Virus: The First Pandemic of the Twenty-First Century

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ABSTRACT. Prior to the 1999 New York City outbreak few had ever heard of West Nile virus. That changed rapidly once the illness caused by the virus resulted in deaths, hospitalizations, and early fears of the unknown etiology of the disease. In some ways it was like Legionnaire's Disease all over again. This review, although not extensive, will cover many of the medical, biological, epidemiological, diagnostic, and public health considerations regarding this new entry onto the list of disease agents seen in the United States.

It is important that each of us is knowledgeable regarding new scientific information. It is all too easy for misinformation to be disseminated to the public by news media and word of mouth. Scientific societies must be ready to protect the public from this misinformation and to add perspective to the issue.

INTRODUCTION

The purpose of this review is to provide the membership of the Ohio Academy of Science who may be unfamiliar with the biological, clinical, and preventive aspects of West Nile virus (WNV) and its infectious process in humans, information that will be both interesting and useful.

Isolation of WNV first occurred in 1937 from an infected person living in the West Nile area of Uganda (Smithburn and others 1940). Since that time, outbreaks have occurred in endemic areas that include Africa, the Middle East, southern Europe, southwest and central Asia, and Oceania (Mandell and others 2000). The virus is most commonly transmitted by mosquitoes of the genus Culex (Brooks and others 2001). After being bitten by an infected female mosquito, the virus spreads throughout the body of the human host. If symptoms appear they are typically an acute, usually mild febrile disease often accompanied by malaise, anorexia, nausea, vomiting, and headache (Table 1). Transient meningeal involvement may occur at this time. Fatal cases associated with severe neurological manifestations have been seen in the elderly or debilitated person (Table 2). Until 1999, this was our understanding of West Nile virus and the associated infection. At that time the virus caused an outbreak in New York City (Nash and others 2001). It should not be surprising that since 1999, our knowledge of West Nile virus has increased as the virus has spread across the country.

WHAT IS WEST NILE VIRUS?

West Nile fever is caused by an arbovirus of the family Flaviviridae and the genus Flavivirus (Brooks and others 2001). The virus is commonly called West Nile virus. The virus is spherical, with a diameter of about 50.0 nm. The nucleic acid is single-stranded RNA with a positive sense (that is, the viral RNA acts like a messenger RNA in host cells). The virus has a viral hemagglutinin (E-glycoprotein) that is involved in host cell attachment. This hemagglutinin can stimulate neutralizing antibodies (Mandell and others 2000; Petersen and Marfin 2002).

WNV is closely related antigenically with Japanese encephalitis and St. Louis encephalitis. This can lead to laboratory misdiagnoses (discussed later). The virus, like other Flaviviridae viruses, replicates in the host cell's cytoplasm and virus particles assemble at the host's endoplasmic reticulum. Once whole virus is assembled, infection can spread to other cells of the host.

THE ENZOOTIC CYCLE

The reservoir of the virus appears to be within various bird populations. In the United States this reservoir seems to be most extensive in crows, although other birds such as Blue Jays have been implicated (MMWR
Clinical Characteristics of Presenting Patients

- **Incubation period:** 3-15 days
- **Subclinical:** 99%
- **Disease:** Encephalitis with profound muscle weakness
- **Mortality:** Approx. 10% (age >75)
- **Disease Risks:** Elderly, Diabetes, Outdoor Activity

**Syndromes**

- Encephalitis with Weakness
- Encephalitis without Weakness
- Aseptic Meningitis
- Fever and Headache

**Percent of Patients Presenting**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis with Weakness</td>
<td>34.0</td>
</tr>
<tr>
<td>Encephalitis without Weakness</td>
<td>29.0</td>
</tr>
<tr>
<td>Aseptic Meningitis</td>
<td>29.0</td>
</tr>
<tr>
<td>Fever and Headache</td>
<td>8.0</td>
</tr>
</tbody>
</table>

**Laboratory Study**

<table>
<thead>
<tr>
<th>Laboratory Study</th>
<th>Value (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal Fluid</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>104 (15-45 mg/100 ml)***</td>
</tr>
<tr>
<td>WBC</td>
<td>38 (0-10/cu mm)***</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>47% (0.0%)***</td>
</tr>
<tr>
<td>Glucose</td>
<td>79.8 (45-80 mg/dl)***</td>
</tr>
<tr>
<td>Peripheral White Blood Cells</td>
<td>10,400 (4,500-10,500/cc)</td>
</tr>
</tbody>
</table>


2002a; O'Leary and others 2002). Most birds develop immunity once infected and rarely die from the illness. A number of other vertebrates can be infected with WNV, including chickens and horses (MMWR 2002b), as well as humans. Direct animal-to-human or human-to-human transmissions have not been well documented, except in rare transplant situations (MMWR 2002d) and, possibly, in mother's milk (MMWR 2002e). With the exception of birds, infection of other hosts appears to be coincidental.

The enzootic cycle is relatively straightforward. During the spring and summer months, female *Culex* sp. of mosquitoes take a blood meal from an infected vertebrate host, usually a bird. After picking up the virus they can readily transmit the virus to a susceptible host at the next blood meal. Other genera of mosquitoes and insects (sand flies and ticks) may also act as vectors (Turell and others 2001). Although mosquitoes tend to be somewhat species-specific regarding blood meals, they can become more cosmopolitan under certain circumstances. When humans become the incidental blood source for infected mosquitoes and so become infected, the outbreak gets our attention. The "bird(to other host)-to-mosquito" cycle seems to continue throughout the spring and summer months, ending as the weather gets cold and mosquito activity ceases. How the virus over-winters has been open to discussion. Studies of birds along the usual eastern and midwestern north-south flyways appear to indicate that birds carry the virus to warmer climates over the winter months (O'Leary and others 2002). The virus has been detected in birds as far north as Canada and as far south as the Caribbean.

**THE US EXPERIENCE**

In late August of 1999, a number of cases of encephalitis were detected in the New York City borough of Queens (Table 2). An excellent job of public health, medical diagnosis, and environmental epidemiology eventually resulted in isolation and identification of West Nile virus from persons who contracted the disease and also from animal sources (Lopez 2002). From that time until now, WNV has spread throughout much of the United States. It is interesting to note that isolates from the US appear to be strongly related, genetically, to isolates from Israel that were prominent there from 1997 to 2000 (Giladi and others 2001). The relationship of the two sets of isolates was approximately 99.8% using reverse transcription-polymerase chain reaction data. Whether this Israeli homolog was the source of the virus that appeared in the US in 1999 is unknown. (This homolog appears elsewhere in the Middle East as well, but rarely is epidemiological testing done in the area.) Also unknown is how the virus got into the United States.

Another interesting aspect of the US isolates is that although they cause the same symptoms as any classical case of West Nile from the original endemic areas in Africa, Asia, the Middle East and Europe, there seems to be a slightly higher morbidity rate, although death is still very uncommon (Mostashari and others 2001). From 1 January to 4 October 2002 there have been a total of 2,631 laboratory-confirmed cases of WNV infection reported to the Centers for Disease Control and Prevention.
(CDC 2002b). Of this group, there were 136 deaths attributed to West Nile. Thus the apparent death rate is 52 deaths per 1000 clinical cases for all ages. Death rates approaching 200 deaths per 1000 clinical cases are not uncommon in the population over 70 years of age (Petersen and Marfin 2002). Most cases go undiagnosed, so that the above statistics are skewed.

**CLINICAL MANIFESTATIONS**

The incubation period for West Nile is 3 to 15 days after infection of the human host. Most patients infected with WNV are asymptomatic and therefore have no clinical evidence of disease (Table 2). Symptoms appear in about 20% of those infected and usually last 3 to 6 days. These usually appear as the mild form of the infection—West Nile fever. Persons with West Nile fever usually present with a sudden onset of some or all of the following symptoms: anorexia, eye pain, headache, lymphadenopathy, nausea and/or vomiting, malaise, and myalgia (Mostashari and others 2001). The frequency of various symptoms and signs associated with WNV from the New York outbreak is shown in Table 1. More than 90% of patients hospitalized during this outbreak had fever. Nausea, vomiting, and headache were also common during this outbreak. A skin rash was evident in a minority of patients and was usually described as erythematous, macular, or morbilliform in nature. Only about one person in 150 cases will get the severe neurologic disease. This is about 0.7% of cases. Thus, if 71 deaths have indeed occurred from 1,571 confirmed cases of West Nile infection, a large number of people (50,000 to 100,000 persons) have actually been infected, but with inapparent or no symptoms. Advanced age, especially over 70 years of age, is still the most common risk factor in cases of death from West Nile infection (Nash and others 2001).

A small number of patients have presented with an acute flaccid paralysis associated with a peripheral demyelinating process (Guillain-Barre Syndrome) (MMWR 2002c). The exact etiology of this process has not been well investigated. Research that has been done thus far suggests that the acute flaccid paralysis involves the anterior horn cells of the spinal cord and motor axons, not unlike that seen with acute poliomyelitis (Ohry and others 2001). The frequency of various symptoms and signs associated with WNV from the New York outbreak is shown in Table 1. More than 90% of patients hospitalized during this outbreak had fever. Nausea, vomiting, and headache were also common during this outbreak. A skin rash was evident in a minority of patients and was usually described as erythematous, macular, or morbilliform in nature. Only about one person in 150 cases will get the severe neurologic disease. This is about 0.7% of cases. Thus, if 71 deaths have indeed occurred from 1,571 confirmed cases of West Nile infection, a large number of people (50,000 to 100,000 persons) have actually been infected, but with inapparent or no symptoms. Advanced age, especially over 70 years of age, is still the most common risk factor in cases of death from West Nile infection (Nash and others 2001).

Another recent development regarding WNV has been the appearance of the agent in organ donor tissue (MMWR 2002c) transplanted into recipients and in transfusion recipients. These situations are currently under public health scrutiny and are rather worrisome. At least four persons received transplanted tissue from one WNV infected donor. One of these recipients died of WNV disease and the others appear to be recovering. The CDC has reports of patients receiving blood products that may have been infected with WNV (MMWR 2002c).

There are two viruses that are somewhat similar to WNV, and should be mentioned at this time. St. Louis encephalitis (SLE) is very similar to WNV in that it is in the same family as WSN (Flaviviridae) and causes similar symptoms. The vector (Culex mosquitoes) and the reservoirs are similar to WNV. About 125 cases of SLE are reported per year. Although outbreaks of SLE occur throughout the United States, most occur in the Midwest and South (CDC 2002c). WNV and SLE can be differentiated through serological testing. The second virus that is similar to WNV is La Crosse encephalitis (LCE). However, LCE is a member of the family Bunyaviridae. This family differs structurally, antigenically, and in the way it replicates from the Flaviviridae. LCE causes outbreaks of encephalitis most commonly in the Mississippi and Ohio River valleys (CDC 2002d). The vector is usually woodland mosquitoes (for example, Aedes spp.). Small mammals, such as squirrels, chip-munks and rabbits, are the reservoir. As such, most outbreaks are not urban in nature but rural. Only about 100 cases are reported each year and most of these in persons under 20 years of age. Interestingly, La Crosse is related to the Hantavirus group. WNV and LCE differ serologically.

**DIAGNOSIS, TREATMENT, AND PREVENTION**

Diagnosis is initially made by identification of symptoms and confirmed by laboratory workup. Laboratory diagnosis consists of tests to detect antibodies against virus or viral nucleic acid in serum and/or spinal fluid. The optimal serologic method to detect these antibodies is an IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Persons infected less than 8 days prior to the test may not be positive. Persons with a prior exposure (within about six months) to WNV may also be positive, as well as those vaccinated for or infected with a different flavivirus, such as yellow fever, Japanese encephalitis, or dengue. A plaque reduction neutralization test may be useful in identifying false-positive MAC-ELISA test specimens (Martin 2002). Results of nucleic acid amplification (PCR) testing have been positive in up to 55% of CSF samples and in 10% of serum samples from patients with WNV (NYDH 2001). The CDC may perform a plaque reduction neutralization test (PRNT) on specimens under certain conditions, to assist in a confirmatory diagnosis (CDC 2002a). Persons who present with a four-fold increase in acute versus convalescent serum titers of antibody against WNV antigen are considered confirmed cases (CDC 2002e).

There is as yet no documented effective direct treatment for this virus—not unlike many viral infections. Treatment generally is supportive care; however, interferon alpha-2b and ribavirin have been suggested as a possible treatment in severe cases of West Nile encephalitis (Anderson and Rahal 2002). At this time there is no controlled study data to support the use of these agents. There is no vaccine currently available for human use. A vaccine does exist for horses, which are especially susceptible to West Nile infection, with a 40% mortality rate in cases where symptoms occur. Even so, most horses do recover. Other vaccines for various forms of equine encephalitis (for horses) do not protect from West Nile infection.
Obviously the best “treatment” is to never come in contact with an infected mosquito. To accomplish this, one needs to take personal care to use insect repellents (Fradin 1998) and avoid the mosquito vector’s habitat—regions near standing bodies of water. In a recent article, Fradin and Day (2002) indicate that DEET-based repellents may be superior to other repellents in repelling mosquitoes that carry WNV. In another article by Pollack and others (2002), the authors specifically caution against the use of botanical repellents and certain devices marketed as insect repellents or attractants. Use of screens in windows and use of clothing covering the body when outside are helpful in preventing insect bites, especially when used with appropriate repellents. Persons should watch the time of day they plan activities. Early morning or late evening activities should be avoided because of high mosquito activity at those times. Area Public Health Departments usually include periodical spraying for insects and, when possible, use of larvicides. Homeowners can assist by spraying appropriately when insects become numerous in their yards and by removing potential mosquito breeding areas such as standing water or old tires where standing water can accumulate.

AFTERWORD

Although West Nile is a new, interesting, and indeed clinically important consideration, its impact should not be over-emphasized. When people die from an infection, it is a concern to all. However, the death rates due to infections from this organism have been relatively low when compared to such viral infections as influenza. While it is certainly important to direct attention to WNV, we must not reduce our efforts to encourage appropriate immunizations for other serious infections. The national media tends to exaggerate and over-emphasize new diseases and infections (Anonymous 2002). It is up to members of scientific societies to give perspective to news accounts of such situations. Members of the Ohio Academy of Science should provide such perspective when needed.

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