WEST NILE VIRUS: Epidemiology and Clinical Features of an Emerging Epidemic in the United States

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Abstract West Nile virus (WNV) was first detected in North America in 1999 during an outbreak of encephalitis in New York City. Since then the virus has spread across North America and into Canada, Latin America, and the Caribbean. The largest epidemics of neuroinvasive WNV disease ever reported occurred in the United States in 2002 and 2003. This paper reviews new information on the epidemiology and clinical aspects of WNV disease derived from greatly expanded surveillance and research on WNV during the past six years.

INTRODUCTION

West Nile virus (WNV) was first isolated from the blood of a febrile woman in the West Nile province of Uganda in 1937 (1). This mosquito-borne virus has been recognized as the cause of epidemics of febrile illness and sporadic encephalitis in Africa, the Mediterranean Basin, Europe, India, and Australia (2, 3). In 1996 WNV caused a large outbreak of encephalitis in Romania, and in 1999 the virus was detected in the Western Hemisphere for the first time during an outbreak of encephalitis in New York City (4, 5). Since then, WNV has spread dramatically across North America and southward into Latin America and the Caribbean (Figure 1) (5a, 5b). This review describes epidemiologic and clinical information regarding WNV disease derived from the rapid expansion of WNV research in the past six years.

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**Epidemiology**

WNV is transmitted to humans through the bite of infected mosquitoes that acquire the virus after feeding on vertebrate amplifying hosts, most likely birds. During epidemics in Africa, infection attack rates have reached as high as 55%, but in the United States <3% of affected populations have acquired infection during epidemic transmission (6–8). The intensity of transmission to humans depends on the numbers and feeding behavior of infected mosquitoes and on local ecologic determinants of human exposure to mosquitoes. In the United States, the principal mosquito vectors are *Culex pipiens*, *C. restuans*, *C. quinquefasciatus*, and *C. tarsalis*, but other species may contribute to localized foci of transmission (9–12). WNV is transmitted vertically from female *C. pipiens* mosquitoes to the next generation, and it can overwinter in hibernating female mosquitoes, thus providing the mechanism for persistence of the virus through cold winters and reemergence in the spring (13, 14).

Birds, particularly corvids (crows, magpies, and jays), house sparrows, house finches, and grackles, appear to be highly competent reservoirs for mosquito infection with WNV (9, 15). WNV has presumably spread in the Western Hemisphere through the movement and migration of birds, although this has not been conclusively proven (16, 17). Alligators may also serve as competent reservoirs in the southeastern United States (18). Most mammals, including humans, do not appear to develop high enough titers of WNV in the blood to infect mosquitoes, but the potential contribution of mammals to WNV transmission needs further study (11, 19, 20).
TABLE 1  Human West Nile virus disease cases by clinical syndrome, United States, 1999–2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Total cases</th>
<th>Neuroinvasive cases</th>
<th>West Nile fever cases</th>
<th>Other clinical/unspecified</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>62</td>
<td>59</td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>2000</td>
<td>21</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2001</td>
<td>66</td>
<td>64</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>2002</td>
<td>4156</td>
<td>2946</td>
<td>1162</td>
<td>48</td>
<td>284</td>
</tr>
<tr>
<td>2003</td>
<td>9862</td>
<td>2866</td>
<td>6830</td>
<td>166</td>
<td>264</td>
</tr>
<tr>
<td>2004*</td>
<td>2539</td>
<td>1142</td>
<td>1269</td>
<td>128</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>16,706</td>
<td>7096</td>
<td>9268</td>
<td>342</td>
<td>666</td>
</tr>
</tbody>
</table>

*Reported to CDC as of April 29, 2005.

Transmission of WNV in North America increases during the warmer months, with peak activity from July through October (21). From 1999 through 2004, 16,706 cases of human WNV disease were reported in the United States with onset of illness as early as April and as late as December. Of these 16,706 cases, 7096 were reported to be neuroinvasive disease, 9268 were West Nile fever (WNF), and 342 had unspecified or other clinical presentations (Table 1). There were 666 reported deaths due to WNV over the same period. (Updates on reported human cases can be found at http://www.cdc.gov/ncidod/dvbid/westnile/index.htm.)

The incidence of neuroinvasive disease and death due to WNV increases with age, is slightly higher among males (Figure 2), and is higher among immunosuppressed recipients of transplanted organs (21–23). It is still unclear whether other immunocompromised people are at higher risk of severe WNV disease, but severe WNV disease in patients with history of malignancies has been described (24–27). Diabetes, hypertension, and cerebrovascular disease have also been considered as possible risk factors (5, 21, 28, 29). A gene for flavivirus resistance has been found in mice but has not yet been shown to play a role in human disease (30, 31).

In 2002, several mechanisms of WNV transmission were recognized for the first time. WNV was transmitted through blood transfusions, organ transplantation, trans-placentally, and possibly through breastfeeding (32–35). Other instances of non-mosquito-borne transmission include laboratory-acquired infections, possible aerosol transmission to workers at a turkey farm, and possible transmission through dialysis (36–38).

**VIROLOGIC CHARACTERISTICS AND PATHOGENESIS**

WNV is an arbovirus belonging to the family Flaviridae. It is an enveloped, spherical virus about 50 nm in diameter containing a single strand of RNA that encodes structural capsid (C) protein, envelope (E) protein, and premembrane (prM) protein, as well as seven nonstructural proteins (39). The E protein binds to as yet
unidentified cell receptors and stimulates neutralizing antibody response; conformational changes in this protein affect WNV virulence (40). WNV is antigenically related to Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus.

Genetic sequencing of WNV has identified two lineages; lineage 1 includes pathogenic strains from North America, Europe, Australia, Africa, and Asia, whereas lineage 2 includes only strains from Africa (including the original Uganda strain) and Madagascar that do not tend to cause severe human disease (41). Lineage 1 comprises four clades: Indian, Kunjin, A, and B (which includes an isolate from India) (42). Isolates from the United States are in clade B of lineage 1 and are closely related to strains from Israel; all strains in this clade are virulent in mice. The other clades in lineage 1 comprise both attenuated and virulent strains, as does lineage 2 (42). The WNV strain isolated in 1999 in New York is more virulent in American crows than are strains from Australia and Kenya, and more virulent in sparrows than an Australian strain (43, 44). Initially there appeared to be little genetic modification of WNV strains in North America, but isolates from Texas and Mexico have been found to be attenuated, apparently because of mutations in nonstructural proteins and the E protein (42, 45, 46).

It is believed that WNV replicates in dendritic cells at the site of inoculation and then spreads to regional lymph nodes and thence to the bloodstream (47). Experiments in mice indicate that binding of double-stranded WNV RNA to
toll-like receptor-3 induces production of tumor necrosis factor alpha, which increases permeability of the blood-brain barrier and allows viral penetration of the central nervous system (CNS) (48). WNV directly invades neurons, particularly cells in the brainstem, deep nuclei of the brain, and anterior horn cells in the spinal cord (30, 49, 50). In addition to destruction of infected nerve cells, collateral damage to bystander cells or immune-mediated damage might contribute to neurologic symptoms (51–53). Genetic susceptibility to flaviviral disease in mice is thought to involve deficient production of 2'-5'-oligoadenylate synthetase, but to date genetic susceptibility has not been demonstrated in humans (30, 31).

Histopathologic examination of tissues from patients with WNV neuroinvasive disease shows neuronal loss, perivascular inflammation, microglial nodules, and neuronophagia with pathologic changes concentrated in the brainstem, deep gray nuclei, and anterior horns of the spinal cells (49, 50, 54). In two fatal cases, there was a predominance of CD8+ T cells in the inflammatory infiltrate found in CNS parenchymal tissues (55). Studies in mice have suggested that CD8+ T cells are involved in both the immunopathology of, and recovery from, WNV infection (56). Muscle biopsies of patients with paralysis have demonstrated scattered necrosis of muscle fibers with focal invasion of macrophages but without substantial inflammation, as well as perivascular inflammation of small vessels (26).

CLINICAL MANIFESTATIONS

About 80% of WNV infections are asymptomatic, 20% result in self-limited West Nile fever (WNF), and <1% result in neuroinvasive disease (encephalitis, meningitis, or flaccid paralysis) (7). Symptomatic illness develops 2–14 days after virus inoculation (39). WNF is characterized by the acute onset of fever, headache, malaise, fatigue, weakness, muscle pain, and difficulty concentrating (2, 57). Roughly a quarter to a third of patients report vomiting or diarrhea, and a quarter to a half have a rash (57, 58). Whereas some cases of WNF resolve within a week, more severe cases have persistent fatigue and muscle weakness for a month or more (57). Rare cases of WNV-associated hepatitis, pancreatitis, myocarditis, cardiac dysrhythmia, rhabdomyolysis, orchitis, uveitis, vitritis, and optic neuritis have been reported (54, 59–66). Chorioretinitis may be more common during WNV infection than previously thought (67).

Presenting signs and symptoms of WNV neuroinvasive disease include fever in roughly 70%–100% of patients, headache in 50%–90%, vomiting in 30%–75%, diarrhea in 15%–35%, and rash in 5%–50% (5, 29, 54, 68–74). Other commonly reported symptoms include muscle aches, weakness, altered mental status, fatigue, nausea, back pain, and stiff neck. Patients with encephalitis may have movement disorders including Parkinsonism and tremors (54, 69). Some patients may present with a clinical picture of sepsis (hypotension, tachycardia, tachypnea, fever, and rigors) (70). Chorioretinitis was found in 20 (69%) of 29 patients seen at a hospital in Tunisia with WNV illness ranging from fever with headache to severe neurologic disease (67).
WNV infection of spinal anterior horn motor neurons causes flaccid paralysis similar to poliomyelitis, sometimes without any overt manifestations of meningitis or encephalitis (26, 54, 75). Onset of paralysis may be isolated to one limb or multiple limbs, is usually asymmetric, and may involve cranial nerves (26, 54). Paralysis of respiratory muscles may require mechanical ventilation, and some patients may have bladder and bowel dysfunction (53, 69). Patients with anterior horn cell disease have pleocytosis in cerebrospinal fluid (CSF). Their electrodiagnostic tests demonstrate decreased compound muscle action potentials and evidence of denervation but preserved or decreased sensory nerve action potentials and relatively preserved nerve conduction velocities without evidence of demyelination (26, 54, 75–77). Rarely, patients with WNV infection may develop Guillain-Barré syndrome, characterized by inflammatory demyelinating polyradiculoneuropathy (24, 78). Patients with Guillain-Barré syndrome usually have elevated CSF protein with few cells in the CSF (albuminocytologic dissociation), and electrodiagnostic tests indicate damage to peripheral myelin (76).

A variety of clinical laboratory abnormalities have been described in patients with WNV infection. CSF from patients with neuroinvasive disease can have from <10 to >1000 leukocytes/mm³ and often shows a predominance of neutrophilic cells early in the infection followed by a shift to lymphocytosis (26, 54, 70). The lymphocytes in CSF may resemble plasma cells or Mollaret cells (79, 79a). CSF protein levels are usually elevated, but glucose levels tend to be normal (26, 54). Peripheral blood counts can be normal or show anemia, thrombocytopenia, leukocytosis, leukopenia, or relative lymphopenia (5, 26, 29, 75, 80). Elevated creatine kinase has been described in some patients, some patients may have hyponatremia, and one report has described elevated serum ferritin late in the course of WNV disease (24, 26, 54, 62a, 81). T2-weighted MRI of the brain can be normal or show increased signal density in the leptomeninges, cortex, subcortical white matter, brainstem, cerebellar vermis, thalamus, or deep nuclei such as the substantia nigra (5, 24, 54, 69, 70, 75). T2-weighted MRI images of the spine can be normal or show abnormal signal density in the anterior horns or cauda equina (24, 26, 54, 69).

DIAGNOSIS

WNV infection should be considered in the differential diagnosis of any patient in an enzootic area (Figure 1) with an acute febrile or neurologic illness who has been recently exposed to mosquitoes, or who has received a recent blood transfusion or organ donation. Serum should be tested for the presence of class M immunoglobulin (IgM) antibody to WNV, which generally indicates recent infection. The IgM test is usually done by enzyme immunosorbent assay (ELISA), which may cross-react with antibody to other flaviviruses. In the setting of a WNV outbreak, the positive predictive value of a positive IgM ELISA to WNV is high but still should be confirmed by WNV plaque-reduction neutralization assay on paired sera if possible (82). Where exposure to other flaviviruses is possible, or
if the clinical presentation is sporadic or unusual, a neutralization assay should be performed to help distinguish the infecting flavivirus. A second serum sample collected two to three weeks after the first can help confirm acute infection by showing a fourfold change in WNV-specific neutralizing antibody titer. If there are signs of CNS involvement, CSF should also be tested for WNV antibody by ELISA. Both serum and CSF can be tested for the presence of WNV nucleic acid; however, because of limited sensitivity, a positive test provides convincing evidence of WNV infection but a negative test does not rule out WNV infection (83).

PROGNOSIS

Patients with milder forms of WNF often recover after several days of illness, but those with more severe illness experience fatigue, weakness, and aching that can last for weeks or months (57, 69, 84). Most patients with WNV meningitis and no focal neurologic deficits will recover completely (69). The prognoses for WNV encephalitis and WNV flaccid paralysis are poor, and severe neurologic deficits often persist for months or are lifelong (69, 70, 84). In one follow-up study, only 13 (17%) of 35 patients hospitalized for WNV illness reported full recovery 12 months after their onset of illness (84). Another report of four cases of flaccid paralysis due to WNV infection suggested that strength can improve with months of rehabilitation, but even this report documented persistence of profound limb weakness (85). In cases of transient dysfunction rather than profound destruction of anterior horn cells, there could be selective improvement in muscle function (76, 86). A study of 14 patients with WNV infection indicated that those with normal MRIs or with abnormalities noted only on diffusion-weighted images had better outcomes than those with abnormalities on fluid-attenuated inversion recovery images and T2-weighted images (87).

TREATMENT

To date, no specific treatment for WNV disease has been identified. Interferon alpha, corticosteroids, and WNV-specific immunoglobulin have been given to selected patients, but the determination of efficacy of any of these treatments awaits results of clinical trials (29, 53, 74). An antisense nucleic acid compound intended to inhibit WNV replication has been tested in humans and is being evaluated in a clinical trial (79). Ribavirin was administered to some patients during a WNV outbreak in Israel in 2000, but treated patients did not appear to fare any better than untreated patients (29). A study of neurotropic Sindbis virus infection in rodents suggested that enhancement of glutamate transport near infected spinal cord neurons might protect against collateral damage to neighboring nerve cells; whether this finding might help in developing treatment of WNV disease awaits further research (51, 53). Experiments in mice raise the possibility that antagonists to tumor necrosis factor alpha might prevent WNV invasion of the CNS (48, 88).
PREVENTION AND CONTROL

WNV infection can be prevented by avoiding exposure to infected mosquitoes. Coordinated mosquito control programs that eliminate mosquito breeding sites, apply larvicides to breeding areas, and spray pesticides targeted at adult mosquitoes can reduce their abundance, but the impact of such programs on human disease depends on multiple ecologic determinants of mosquito abundance and human exposure to mosquitoes (89, 90). To reduce their exposure to mosquito bites, people should wear insect repellent on skin and clothes and avoid being outdoors during hours of peak feeding by WNV mosquito vectors, usually from dusk to dawn. Repellents containing N,N-diethyl-m-toluamide (DEET) have excellent safety records and are effective (91–93). Oil of lemon eucalyptus, soybean oil, and picaridin also appear to provide effective protection (91, 94). Permethrin is effective when applied to clothing (94a).

Blood donations in WNV endemic areas should be screened for evidence of WNV infection to prevent transmission of WNV through blood transfusions (95). Screening deceased organ donors for WNV infection has not been implemented because of concern that life-saving organs in scarce supply will be inappropriately rejected in the event of false-positive WNV screening tests (96).

Research toward an effective vaccine to prevent WNV disease in humans is rapidly expanding. Both an inactivated WNV vaccine and a recombinant vaccine based on canarypox expression of WNV antigens are currently licensed for use in horses (97, 98). Vaccine candidates for use in humans include an inactivated WNV vaccine, an attenuated WNV vaccine, chimeric live virus vaccines that incorporate WNV E and preM genetic sequences into a 17-D yellow fever vaccine or serotype-4 dengue virus backbone, DNA vaccines that elicit WNV antigen or attenuated Kunjin virus antigen expression, and a recombinant vaccine that uses measles vaccine as a vector for WNV antigens (99–104). Thus far, only the chimeric vaccine using a yellow fever 17-D vaccine backbone has been tested in clinical trials in humans (99).

SUMMARY

The introduction of WNV to the Western Hemisphere has had a dramatic impact on public health and clinical practice in the United States. Concurrent with its spread across the continent, expanded research has provided new information on the virology, pathogenesis, diagnosis, and transmission dynamics of this previously obscure virus. WNV disease must now be included in the differential diagnosis of patients with acute febrile or neurologic disease in the United States, Canada, Mexico, Central America, and the Caribbean, and is likely to be a persistent public health concern for years to come. Exploration of new treatment and prevention strategies, including the development of vaccines, is under way. However, at present, personal protection against mosquito bites, reducing abundance of mosquito vectors, and
screening the nation’s blood supply for WNV nucleic acid are the cornerstones for preventing WNV disease.

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