West Nile Virus Infection in the United States

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West Nile virus (WNV), an arthropod-borne flavivirus belonging to the Japanese encephalitis virus antigenic complex, first appeared as a cause of naturally acquired meningitis and encephalitis in the United States in the New York City area in the summer of 1999. During succeeding years, the virus has spread rapidly throughout North America, becoming enzootic in bird and mosquito populations throughout much of the continental United States. In 2003, WNV was responsible for one of the largest arboviral encephalitis epidemics in US history (9858 cases; 2863 with meningoencephalitis and 262 deaths) and one of the largest WNV meningoencephalitis epidemics yet recorded.

**EPIDEMIOLOGY AND ECOLOGY**

The vast majority of human infections are caused by the bite of an infected mosquito, typically of the *Culex* genus. Human infection occurs predominantly between June and November, with a peak between mid-July and mid-September, reflecting the seasonal activity cycle of mosquito vectors. Wild birds serve as the natural reservoir and amplifying hosts. Oral and cloacal shedding of the virus has been documented in birds, and vector-independent avian infection can be documented after close contact with infected birds or after feeding birds infected material, although the relative importance of mosquito-dependent and mosquito-independent transmission under natural circumstances remains unknown. Although more than 100 bird species are known to be susceptible to WNV infection, *Corvid* species appear to be particularly important hosts, and deaths in crows, ravens, sparrows, and jays frequently precede outbreaks of human infection. Equine cases typically coincide with human illness, rather than serving as sentinel infections.

West Nile virus is unique among arboviruses both in its capacity to infect an unprecedented number of mosquito species and in the facility with which infection can be initiated by nonarthropod-initiated modalities, including blood transfusion, organ transplantation, breast-feeding, transplacental transmission, and laboratory acquisition. Cases of asymptomatic infection outnumber those of symptomatic illness by a ratio of approximately 150:1. Among those symptomatically infected, the most common illness (60%-80% of cases) is West Nile fever. This is an acute self-limited flu-like illness that begins after a 2- to 14-day (average, 6-7 days) incubation period with sudden onset of fever, myalgia, headache, and gastrointestinal disturbance; in a variable percentage of cases, the illness is associated with arthralgia, a red maculopapular nondesquamating rash, lymphadenopathy, retroorbital pain, and persisting fatigue. A subset of symptomatic patients develops neurological illness, which can take the form of aseptic meningitis, encephalitis, acute flaccid paralysis (AFP), or, in many cases, a combination of these syndromes.

**SEROLOGY AND DIAGNOSIS**

Diagnosis of both neurological and nonneurological WNV infection depends largely on serologic examination. Viremia is typi-
cally short lived, precedes the onset of symptoms, and is cleared by the time a patient becomes symptomatic. As a result, serum nucleic acid amplification tests, including polymerase chain reaction (PCR), are not of utility in acute clinical diagnosis but play an important role in ensuring that blood products donated by asymptomatic individuals are not WNV-infected. Demonstration of WNV-specific IgM antibody remains the mainstay of diagnosis, and it is rapidly accomplished using commercially available antibody-capture enzyme-linked immunoassays. Infection with other members of the Japanese encephalitis serocomplex (eg, St Louis encephalitis virus [SLEV] and Japanese encephalitis virus [JEV]) can induce antibody responses that cross-react with WNV. When such heterologous antibody responses are present, they are less intense than homologous antibody responses against the infecting agent and rarely include significant titers of cross-reacting neutralizing antibody. Determination of concomitant IgM titers against other Japanese encephalitis serocomplex members and measurement of plaque reduction neutralization titers against WNV are usually sufficient to establish the specificity of the antibody response in ambiguous cases. It is also critical to obtain a history of vaccination (eg, against Japanese encephalitis or yellow fever viruses) and foreign travel (eg, to East Asia or other areas in which Japanese encephalitis or dengue is endemic), as well as a prior history of meningitis or encephalitis. Demonstration of WNV IgM antibodies in the cerebrospinal fluid (CSF) is essentially diagnostic of WNV-associated central nervous system (CNS) infection because IgM antibodies do not cross the blood-brain barrier, and their presence in CSF is therefore indicative of intrathecal synthesis stemming from local antigen exposure. In addition to providing an important diagnostic marker, IgM antibodies appear to play a critical role in protection against WNV infection in experimental models. Amplification of WNV nucleic acid from CSF by PCR testing is highly specific, but PCR is less sensitive than serologic testing because results of PCR are positive in approximately only 70% of specimens with demonstrable IgM antibodies. Serologic tests must always be considered in terms of the timing of specimen collection in relation to illness. Although CSF IgM antibodies are found in more than 90% of patients with WNV-associated CNS disease by day 8 of illness, testing within the first 72 hours may yield negative results with subsequent seroconversion. The duration of positive IgM responses in serum and CSF has not yet been fully characterized. Preliminary studies suggest that approximately three fourths of patients have persisting IgM antibody responses 1 year postinfection, an issue that may confound interpretation of serologic results in the future.

CSF, NEUROIMAGING, AND ELECTROENCEPHALOGRAPHY

Almost all patients with neurological WNV infection will undergo CSF analysis and have neuroimaging studies performed. Typical CSF findings include a pleocytosis with elevated protein and normal glucose levels. Patients can have either lymphocyte or polymorphonuclear predominance. The degree of pleocytosis is extremely variable. In most series, the mean cell count for patients with meningitis or encephalitis has ranged between 24 cells/mm³ and 308 cells/mm³, although counts exceeding 2000 cells/mm³ have been reported. Unlike other viral infections in which a polymorphonuclear predominance when present typically shifts to lymphocytes within 24 to 48 hours, in WNV polymorphonuclear neutrophils may persist through the first week. Cerebrospinal fluid lymphocytes are often reactive appearing and may resemble plasma cells or even Mollaret cells. Results from computed tomographic scans are typically normal in patients with WNV CNS disease. Abnormal magnetic resonance imaging findings have been reported in approximately one third of cases, although the need for more detailed analysis of magnetic resonance imaging abnormalities and protocols has recently been emphasized. Reported findings have included areas of increased signal on T2-weighted and fluid-attenuation inversion recovery images in the basal ganglia, thalamus, substantia nigra, and brainstem. Fluid-attenuation inversion recovery and diffusion-weighted imaging sequences may show hyperintense signal with decreased apparent diffusion coefficient values in the early stages of illness, even when conventional magnetic resonance imaging sequences are normal. Subcortical white matter abnormalities may be present but are of uncertain specificity. Leptomeningeal enhancement is variably seen. In patients with AFP, signal abnormalities in the cord, including the anterior horns, conus, cauda equina, and nerve

Figure 1. Magnetic resonance imaging of West Nile virus encephalitis. Axial T2-weighted image (repetition time, 5500; echo time, 105; repetitions, 2) at the level of the thalami. There is patchy increased signal within both thalami (arrows). Areas of increased signal, not seen in prior studies, also occur within the white matter bilaterally. Figure courtesy of Edward J. Escott, MD, Department of Radiology, Section of Neuroradiology, University of Colorado Health Sciences Center, Denver.
roots, have been reported, although in the majority of cases, results of imaging studies are normal. Electroencephalographic findings are normal in patients with meningitis, but abnormalities occur in the majority of patients with encephalitis. The most common features include diffuse irregular slowing (60%-100% of cases), which may be more prominent in frontotemporal regions. Less frequently, patients have focal sharp waves or evidence of seizures. Routine laboratory studies are rarely of diagnostic value, although patients may have hyponatremia or lymphopenia, or findings may be suggestive of myositis, pancreatitis, hepatitis, or, more rarely, myocarditis or tubulointerstitial nephritis.

NEUROLOGICAL ILLNESS

During the 2003 epidemic, approximately 69% of cases of symptomatic WNV infection reported to the Centers for Disease Control and Prevention (CDC) were West Nile fever; 29% were neuroinvasive disease, and 2% were unspecified. The CDC did not separately categorize meningitis and encephalitis; however, in Colorado, the state with the largest number of WNV-associated infections (2947), neurological illnesses (622), and fatalities (63) in 2003, it was estimated that approximately two thirds of the neurological cases were meningitis and the remainder were encephalitis. In reports from New York and New Jersey in 1999 and 2000 and Michigan in 2002, the frequency of meningitis ranged between 29% and 42%, and the frequency of encephalitis ranged between 58% and 66%. Weakness was recognized as a cardinal feature of the original New York City epidemic and has been noted in approximately one third to one half of patients with encephalitis in most series. However, it was not until the epidemic of 2002 provided an opportunity to examine a large number of cases that a distinctive clinical syndrome of WNV-associated AFP was identified and subsequently characterized in greater detail.

MENINGITIS AND CRANIAL NERVE PALSY

The clinical features of WNV-associated meningitis resemble those seen in other viral meningitides and include the nearly universal presence of fever, headache, and nuchal rigidity. Neck pain, nausea and/or vomiting, myalgia, and chills or rigors occur in 60% to 80% of cases, and back pain occurs in 40%. Patients with significant alteration in mental status should be considered as having encephalitis rather than meningitis. Unlike other viral meningitides, tremor, which can be postural or kinetic, is frequently seen and has been reported in up to 80% of cases. Myoclonus occurs in approximately 20% of cases. The presence of hyperkinetic movement disorders in a patient with otherwise classic aseptic meningitis, who is examined during a period of WNV activity, should always suggest the possibility of WNV infection. Cranial nerve abnormalities frequently accompany meningitis, and they may be delayed, initially appearing during the second or third week following onset. A similar pattern of involvement may be seen in patients with meningoencephalitis or AFP. The most common cranial neuropathy is peripheral facial paralysis, which may be unilateral or bilateral. Patients frequently complain of transient diplopia, although frank ophthalmoparesis is unusual. Visual blurring may result from chorioretinitis or less commonly optic neuropathy. Dizziness and even true vertigo are other common complaints and may be accompanied by nystagmus. Hearing loss or tinnitus is unusual. Involvement of the brainstem or cranial nerves may result in jaw weakness, dysarthria, and dysphagia. Although some patients with WNV-associated meningitis are reported to have parkinsonian features, including rigidity, bradykinesia, and postural instability, their presence is indicative of parenchymal CNS involvement (encephalitis) rather than uncomplicated meningitis. As noted, patients with meningitis invariably have a CSF pleocytosis, typically with mildly elevated protein and normal glucose levels. Clues that can suggest the possibility of WNV infection include the presence of plasmacytoid lymphocytes and a polymorphonuclear predominance in a patient with an otherwise typical aseptic meningitis and no other evidence to suggest bacterial infection. The age distribution of meningitis cases appears to parallel that for WNV infection, and no specific risk factors have been clearly identified.

ENCEPHALITIS

Most cases of WNV encephalitis are really examples of meningoencephalitis, and they have CSF abnormalities similar to those seen in meningitis cases. Most studies have identified a clear age-related susceptibility to encephalitis, in contrast to meningitis and AFP, with the frequency of encephalitis cases increasing dramatically with increasing age. In a small series, the median age of patients with encephalitis was 70 years (range, 46-81 years), compared with a median age of 35 years (range, 20-39 years) among patients with meningitis. The median age of hospitalized patients in the original New York City epidemic was 71 years, with 88% of patients older than 50 years. Fever (90%-100% of cases), headache (47%-100%), and an altered mental status (46%-100%) are typically present. Although this was not emphasized in the original reports, more recent studies indicate that the majority of patients have postural or kinetic tremor. Signs of parkinsonism, including rigidity, bradykinesia, and postural instability, occur in up to 75% of cases, and myoclonus occurs in approximately 40%. Weakness is often prominent, occurring in at least 50% of cases in most series. These features are unusual in other forms of acute viral encephalitis, with the exception of those caused by other flaviviruses (St Louis encephalitis and Japanese encephalitis), and the presence of such features should always suggest the possibility of WNV infection. In some patients, most signs and symptoms suggest predominant brainstem involvement (brainstem encephalitis) or cerebellar involvement (cerebellitis).

ACUTE FLACCID PARALYSIS

One of the most dramatic WNV-associated neurological syndromes is AFP. Patients typically are initially diagnosed as having acute onset and rapid progression of asymmetric flaccid weakness with associated hyporeflexia or areflexia in involved limbs. It is important to
recognize that this syndrome is not unique to WNV. West Nile virus–associated AFP shares many clinical, laboratory, and pathological features with poliomyelitis, the cardinal neurological infection historically caused by polioviruses and more recently occurring as a rare complication of infection with nonpolio enteroviruses and other viruses. Weakness may involve a single limb, both arms or both legs, or all 4 extremities. Patients with quadripareis or quadriplegia and those with upper-limb involvement may also have associated respiratory insufficiency and commonly require mechanical ventilation. Many patients describe acute aching pain in involved limbs, but paresthesias and/or objective sensory loss is not observed. Bladder and bowel dysfunction occurs in approximately one third of cases. Almost all patients have fever and CSF pleocytosis. Patients can have either a pure AFP syndrome or AFP associated with meningitis or meningoencephalitis. These patients will have additional signs and symptoms, including altered mental status, nuchal rigidity, tremor, and cranial neuropathies. The relative frequency of pure AFP compared with that of AFP in combination with meningoencephalitis is uncertain, although our clinical experience suggests that as many as 50% of patients with encephalitis have some evidence of AFP-like weakness, and a similar percentage of patients with AFP have additional signs or symptoms suggestive of meningitis or encephalitis. Neuroimaging studies are generally unremarkable, although some patients have had abnormalities in the anterior horns, cauda equina or conus, or nerve roots. Electromyographic and nerve conduction studies show reduced or absent amplitude of compound muscle action potentials in involved limbs with normal amplitudes of sensory nerve action potentials. Conduction velocities are normal or minimally reduced proportional to the degree of axonal injury. Electromyographic studies obtained at 3 or more weeks after the onset of illness may show denervation changes in afflicted muscles, including fibrillations, positive sharp waves, and decreased voluntary recruitment. This pattern is consistent with involvement of the motor neurons of their axons. Pathological studies are limited, but in some cases they have shown an acute anterior poliomyelitis. Less frequently, findings from electrophysiologic and imaging studies appear to be more consistent with an acute anterior radiculitis, with magnetic resonance imaging showing enhancement of ventral nerve roots rather than spinal parenchymal abnormalities. Unlike encephalitis, this syndrome does not have a predilection for the elderly, and cases have been reported in adults of all ages; however, in 1 report, it was suggested that younger patients more typically developed monoparesis, whereas older patients (>65 years) more frequently developed paraparesis or quadriparesis. To date, there are no reports of pediatric WNV-associated AFP.

PREVENTION AND TREATMENT

No specific therapy of proven efficacy is available for WNV infection; thus, prevention of infection is of paramount importance. Standard preventive measures include use of DEET(N,N-diethyl-meta-toluamide)-containing mosquito repellents, avoidance of outdoor activities during periods of peak mosquito activity near dawn and dusk, use of protective clothing, and removal of potential mosquito breeding sites by eliminating sources of standing water. Ribavirin inhibits WNV replication and cytopathic effects in cultured neurons in vitro, but it was reportedly of no obvious clinical efficacy in a noncontrolled clinical trial in Israel. Interferon alfa-2b also shows activity against WNV in vitro, and has been used in a nonblinded, nonplacebo-controlled clinical trial, although the design of this study will make determination of efficacy problematic. Interferon alfa-2a was recently shown in a randomized double-blind placebo-controlled trial to lack benefit against Japanese encephalitis, dampening enthusiasm for its use against WNV. A proprietary antisense oligomer (AVI-4020; AVI BioPharma, Portland, Ore), which inhibits WNV replication in vitro, has been tested in a small (9 subjects received the drug) phase 1/2 human clinical trial, and it was found to be safe, although no information about its efficacy is available. Passively transferred anti-WNV antibodies, including an Israeli intravenous immunoglobulin preparation with high titer anti-WNV antibody (Omr-IgG-am; Omrix Biopharmaceuticals Ltd, Tel-Hashomer, Israel), protect mice against WNV infection, and they have been reported to have a benefit in isolated noncontrolled human case reports. A randomized double-blind placebo-controlled trial of Omr-IgG-am compared with a US intravenous immunoglobulin (which lacks detectable anti-WNV antibody) and saline in treatment of WNV encephalitis, sponsored by the Collaborative Antiviral Study group, is currently under way; however, its limited enrollment during the 2003 epidemic means data analysis will not be available until after the 2004 season at the earliest. A crude formalin-inactivated vaccine (Innovator; Fort Dodge Animal Health, Overland Park, Kan) is available for veterinary use and has proven to be safe and efficacious in preventing WNV in horses. Successful human vaccines are already available and in widespread use to protect against both yellow fever virus and Japanese encephalitis virus. Chimeric vaccines, in which WNV genes are inserted into the genetic background of another flavivirus, have also shown protective capacity in primate models of WNV infection. Taken together, these studies indicate a high potential for the successful development of a human WNV vaccine, and initial phase 1 clinical trials of the safety, tolerability, and the immunogenicity of 1 chimeric vaccine (ChimeriVax-West Nile; Acambis, Cambridge, Mass) are already under way. SEQUELAE AND OUTCOME

Data concerning the long-term outcome and sequelae of WNV neurological infection are currently extremely limited. In recent studies, all 5 patients with meningitis had no neurological deficits when reassessed at 8 months postinfection, although some patients complained of residual fatigue, myalgia, and headaches. Five of 7 patients with severe encephalitis (Glasgow Coma Scale score ≤12) recovered to their premorbid level of functioning when reassessed at 8 months postinfection, and this typically occurred within 4 months of infection. Five of 10

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surviving patients with either encephalitis or AFP had some residual postural and/or kinetic tremor and parkinsonism. This was typically mild and did not interfere with daily activities, although one patient had severe kinetic tremor that interfered with eating and grooming, and another had persistent severe parkinsonism. The 3 patients with AFP had the worst overall prognosis and showed no improvement in limb weakness at 8 months. Although bladder symptoms improved, all 3 patients remained wheelchair dependent for ambulation and had electromyographic evidence of chronic denervation with motor axon loss in affected limbs.12

NEUROPATHOLOGY

The overall mortality rate among cases of WNV infection during the large US epidemics of 2002 and 2003 was 2% to 7%, but because almost all deaths occur in patients with encephalitis rather than meningitis or WNV fever, the mortality in this subset is probably 12% to 15% and may reach 35% in those older than 65 years.13 Conversely, pediatric cases of WNV-associated neurological disease are extremely rare and consist of isolated reports of aseptic meningitis,45 rhombencephalitis,46 and meningoencephalitis.47 Only 4 cases of WNV-associated neurological disease remain relatively limited in number,23,25,46,50,51 In cases of encephalitis, the brain shows perivascular parenchymal and meningeal inflammation with neuronal loss, neuropathia, microglial nodules, and astrocyte proliferation (Figure 2).50,53 Inflammatory cells are predominantly T cells (CD3+), with the majority being CD8+ in the parenchyma and either CD8+ or CD4+ in perivascular and meningeal locations.23,33 Similar results have been found in experimental WNV infection in mice, in which CD8+ T cells appear to play a dual role, contributing to both viral clearance and virus-associated immunopathologic features.55 CD68+ cells, including activated microglial cells, are also prominent in areas of neuronal injury.23,27,28 The most severe pathologic changes are frequently confined to the basal ganglia, thalamus, and brainstem, including the substantia nigra. Virus can be isolated from postmortem brain tissue, viral antigen is detectable by immunocytochemistry in infected neurons, and nucleic acid can be amplified by PCR.21,30,52 Patients with AFP who are dying may show a pattern of poliomyelitis, with loss of anterior horn cells, with parenchymal and perivascular inflammation in spinal cord regions innervating affected muscles.22,51,53,56 A similar pattern has been seen in brainstem motor nuclei.22

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