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West Nile Virus Neuroinvasive Disease

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Abstract West Nile virus (WNV), first recognized in North America in 1999, was responsible for the largest arboviral epidemic of human encephalitis in history and continues to be the most frequent cause of epidemic meningoencephalitis in North America. WNV neuroinvasive disease (WNND) occurs in fewer than 1% of infected individuals, with presentations including aseptic meningitis, encephalitis, and poliomyelitis. Between 1999 and 2009, over 12,000 cases of WNND were reported in the United States, with the peak annual incidence occurring in epidemics of 2002 and 2003. In this review, we first summarize the epidemiology of WNV over the past decade and the salient clinical features of WNND, including a discussion of laboratory and radiographic findings, risk factors, morbidity, and mortality. In addition, we review recent progress in our understanding of virus and host determinants of the pathogenesis of WNND, as well as the prospects for the development of specific therapeutic targets.

Keywords West Nile virus · Encephalitis · Poliomyelitis · Acute flaccid paralysis · Meningitis · Meningoencephalitis · Neuroinvasive disease · Vaccine · Treatment · WNND · WNV · Diagnosis

Introduction

West Nile virus (WNV) is an arthropod-borne flavivirus that was first isolated from the blood of a febrile Ugandan woman in 1937. It was subsequently associated primarily with epidemics of flulike febrile illness—and sporadically with encephalitis—throughout Africa, Asia, and Europe. The virus had never been detected in North America before its first US appearance in 1999, but it quickly spread, resulting in the largest epidemic of West Nile neuroinvasive disease (WNND) in US history in 2002 to 2003. Although the bulk of disease due to WNV consists of febrile illness, WNND occurs in approximately 1% of cases, presenting as aseptic meningitis, encephalitis (WNE), or poliomyelitis (WNP) syndrome. WNND remains the leading cause of neuroinvasive arboviral disease in the United States, with significant resultant morbidity and mortality.

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Epidemiology and Transmission

Epidemiology

WNV made its debut in North America in the summer of 1999, with the simultaneous occurrence of an unusual number of deaths of exotic birds and crows in the New York City metropolitan area. These deaths occurred coincidently with an outbreak of 62 cases of encephalitis in humans, which resulted in 7 deaths [1]. Analysis of sequences of genome fragments isolated from dead birds and mosquitoes by reverse-transcriptase polymerase chain reaction (RT-PCR) led to the identification of WNV as the causative agent.

Over the following 3 to 5 years, the geographic range and burden of disease in birds, mosquitoes, and humans rapidly expanded to include the 48 contiguous United States, Canada, Mexico, the Caribbean islands, and Colombia [2]. WNV is a nationally notifiable disease in the United States, with data reported to the Centers for Disease Control

(CDC) through ARboNET, an Internet-based passive surveillance system [3••]. From 1999 through 2008, a total of 28,961 confirmed cases of human WNV disease were reported in the United States, including 11,822 characterized as neuroinvasive, resulting in over 1,100 deaths [3••]. The peak incidence of WNND occurred in 2002 to 2003, with 1.02 cases/100,000 US population. By contrast, the annual incidence rates in 2004 through 2007 stabilized at a lower rate of 0.4/100,000. Continued declines were noted in 2008 and 2009: in 2008, the incidence dropped to 0.2/100,000, and in 2009, only 386 cases of WNND were reported, representing a rate of 0.13/100,000, the lowest rate recorded since 2001 (Fig. 1) [4•]. The reasons for this decline are not entirely clear, but suggested factors have included variations in the populations of mosquito vectors and vertebrate hosts, accumulating immunity in avian amplifying hosts, increased use of personal protective measures, community-level interventions, decreased laboratory diagnosis or reporting, or environmental factors [4•].

Despite the declines in overall incidence noted in the past 5 years, WNV remains the leading cause of neuroinvasive arboviral disease in the United States. To illustrate the magnitude by which WNV exceeds all other causes, for the period from 1999 through 2007, more than 11,000 cases of WNND were reported, whereas a total of only 1,079 cases of reported neuroinvasive disease were due to all other domestic arboviruses (California serotype, St. Louis, Eastern equine, Powassan, Western equine, and Cache Valley combined) [5]. The annual incidence of these domestic arboviruses has not changed significantly since the introduction of WNV in North America.

Transmission

Following its introduction into North America, WNV spread prolifically within birds (>300 species) and has infected an unprecedented number of mosquito species. Corvids (crows, magpies, and jays), house sparrows, house finches, and grackles are particularly competent reservoirs for mosquito infection with WNV. By contrast, mammals (including humans) do not develop sufficiently prolonged or high-level viremia with WNV to play a significant role in transmission. In mosquitoes, WNV can be transmitted vertically and can overwinter in hibernating females, providing the mechanisms for viral persistence and reemergence each spring [2].

Transmission of WNV to humans occurs predominantly following a bite from an infected mosquito, which acquires virus after feeding on vertebrate amplifying hosts, primarily birds [2]. Initial seroprevalence surveys indicated that less than 3% of the populations in endemic areas acquired the infection during epidemic transmission periods, but more recent seroprevalence studies following peak epidemic years have demonstrated higher rates (9.5%–19.7%) in some locales [6].

Although person-to-person transmission does not generally occur, cases have resulted from transfusion of blood products and organ transplantation, as well as following intrauterine, percutaneous (occupational), or breastfeeding exposure. Other isolated reports of possible routes of transmission include respiratory aerosol (workers at a turkey farm) and dialysis [2].

An initial 23 cases of WNV infection via transfusion of blood products (from asymptomatic, viremic donors) reported in 2002 [7] led to the mandate for screening of donor minipools based on nucleic acid amplification; this screening has greatly reduced transmission via this route [8]. Despite these interventions, cases related to transfusion and organ transplantation continue to occur, and health care providers should consider WNND as a possible cause of neurologic complications in patients after blood transfusion [7, 9].

Most infants born to WNV-infected pregnant women are unaffected, but several cases of symptomatic neuroinvasive

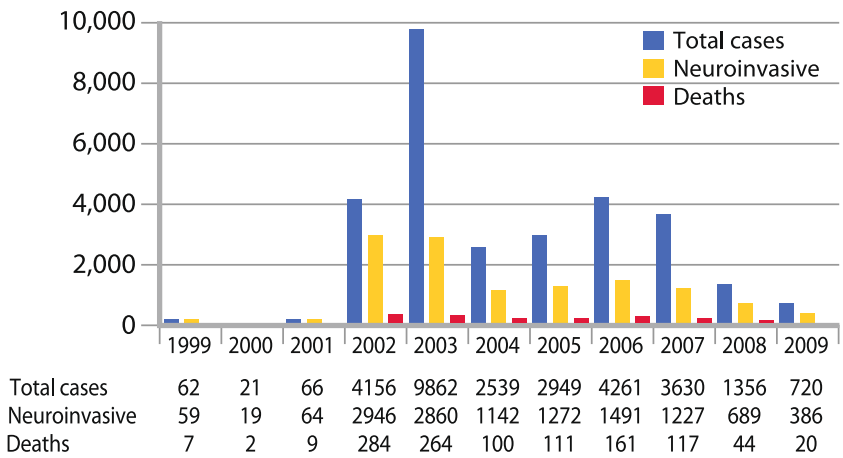

Fig. 1 Annual cases of West Nile virus (WNV) disease, WNV neuroinvasive disease, and deaths attributable to WNV between 1999 and 2009, as reported to the Centers for Disease Control

congenital infection have been reported, including resultant meningitis, encephalitis, chorioretinitis, microcephaly, and intracranial calcifications [10].

Diagnosis

Clinical Features

Fewer than 1% of WNV infections are neuroinvasive. Serologic surveys indicate that for every case of WNV neuroinvasive disease, there are approximately 140 infections; approximately 80% of infected individuals remain asymptomatic and 20% develop clinical infection, termed West Nile fever (WNF), that spares the central nervous system [3••, 4•]. Symptomatic illness develops 2 to 14 days after inoculation. WNF is a self-limited flulike illness characterized by fever, myalgia, headache, and gastrointestinal disturbance (25%–30%), with an associated maculopapular rash in 25% to 50% of cases [11]. Neuroinvasive disease occurs following viremia, after viral penetration of the blood-brain barrier and direct invasion of neurons, particularly those in the brainstem, deep nuclei, and anterior horn of the spinal cord.

WNND presentations are varied and include aseptic meningitis, encephalitis, and poliomyelitis [12–14]. Updated clinical and laboratory criteria for distinguishing neuroinvasive and nonneuroinvasive arboviral disease (including WNV) have been published by the CDC (Table 1). Brainstem encephalitis, cerebellitis, movement disorders, cranial neuropathies, polyneuropathy/radiculopathy, chorioretinitis, and optic neuritis are additional WNV neurologic presentations. The estimated proportion of WNND manifesting as meningitis (35%–40%), encephalitis (55%–60%), or poliomyelitis (5%–10%) has varied within a given epidemic season or locale, and overlap syndromes (e.g., encephalomyelitis) can occur. Children are more likely to present with aseptic meningitis rather than encephalitis as a manifestation of neuroinvasive disease, but all primary manifestations of WNND have occurred in the pediatric population [15, 16••].

Encephalitis

As in other forms of viral encephalitis, nonspecific symptoms such as fever (70%–100%), headache (50%–100%), and altered mental status (50%–100%) are common

Table 1 US Centers for Disease Control (CDC) diagnostic criteria for neuroinvasive arboviral disease

Clinical criteria for diagnosis

Presence of fever and at least one of the following:

- Acutely altered mental status (e.g., disorientation, obtundation, stupor, or coma), **OR**
- Other acute signs of central or peripheral neurologic dysfunction (e.g., paresis or paralysis, nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions, or abnormal movements), **OR**
- Pleocytosis (increased white blood cell concentration in cerebrospinal fluid [CSF]) associated with illness clinically compatible with meningitis (e.g., headache or stiff neck).

Laboratory criteria for diagnosis

- Fourfold or greater virus-specific serum antibody titer, **OR**
- Isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid, **OR**
- Elevated virus-specific immunoglobulin (IgG) antibodies in the acute or convalescent serum specimen, **OR**
- Virus-specific immunoglobulin M (IgM) antibodies demonstrated in serum.

Case classification

A case must meet one or more of the above clinical criteria and one or more of the above laboratory criteria.

Confirmed case:

- Fourfold or greater change in virus-specific serum antibody titer, **OR**
- Isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, CSF, or other body fluid, **OR**
- Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF by antibody capture enzyme immunoassay (EIA), **OR**
- Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same or a later specimen by another serologic assay (e.g., neutralization or hemagglutination inhibition)

Probable case:

- Stable (≤ twofold change) but elevated titer of virus-specific serum antibodies, **OR**
- Virus-specific serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen.

(*From* CDC: Neuroinvasive and Non-Neuroinvasive Domestic Arboviral Diseases, 2004 Case Definition. http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/arboviral_2004.htm. Accessed March 28, 2011)

in West Nile encephalitis (WNE). Vomiting (30%–75%), diarrhea (15%–35%), and rash (5%–50%) are seen in a significant proportion of patients [12–14]. In contrast to other encephalitides, muscle weakness is a prominent finding in 30% to 50% of patients with WNE, often of a lower motor neuron pattern with flaccid paralysis and hyporeflexia, without sensory abnormalities. Other distinctive findings include cranial neuropathies (20%)—commonly unilateral or bilateral peripheral seventh nerve palsy—which may have a delayed onset in the second or third week following the onset of illness [12–14]. Movement disorders (dyskinesias) are common in patients with WNE and can include postural or kinetic tremor (up to 90%), parkinsonism (including cogwheel rigidity, bradykinesia, and postural instability (70%), and myoclonus (20%–40%) [13]. A wide variety of ocular abnormalities have also been reported [17].

Poliomyelitis

The WNV-associated acute flaccid paralysis syndrome, termed West Nile poliomyelitis (WNP), can occur in isolation or in combination with meningitis or encephalitis [18]. The relative frequency of pure WNP compared with WNP combined with encephalitis is uncertain but may be as high as 50%. Unlike WNE, the WNP syndrome does not have a predilection for the elderly and has been reported in all age groups. Patients with WNP have acute onset and rapid progression (within 24–48 h) of asymmetric flaccid weakness, with associated hyporeflexia or areflexia in involved limbs. Motor weakness is usually the result of a poliomyelitis-like process (pure motor deficit due to involvement of anterior horn cells), rather than a Guillain–Barré-like syndrome (motor and sensory deficit involving peripheral nerves), although cases of WVN-associated Guillain–Barré syndrome have also been reported. Weakness can occur in a single limb or in any combination of the four extremities. Respiratory insufficiency may also occur, including respiratory failure requiring endotracheal intubation, as seen in up to 38% of affected patients in a one series [18]. Bowel and bladder dysfunction occurs in one third of patients. Electromyography demonstrates reduced amplitudes of compound muscle action potentials, with normal amplitudes of sensory nerve action potentials. Follow-up studies 3 or more weeks later can show denervation changes [19].

Risk Factors for WNND

Environment

Exposure to infected mosquitoes is the most significant risk factor for acquisition of WNV infection [20]. The risk of acquiring neuroinvasive disease appears to be highest in areas where the primary WNV vectors are *Culex tarsalis* and *Culex quinquefasciatus* mosquitoes [21]. More than 90% of cases occur between July and October [16••]. The five states with the highest incidence of WNND in 2009 were Mississippi, South Dakota, Wyoming, Colorado, and Nebraska [4•]. Illustrating the impact of environmental factors on risk of WNND, twofold increases in neuroinvasive disease were noted in Louisiana and Mississippi following Hurricane Katrina [22].

Host

Age WNND incidence increases with increasing age, with the highest incidence noted among those older than 70 years of age [4•]. WNND is less common in children than in adults [16••, 23]. Children accounted for only 4% of all WNND case subjects reported from 1999 to 2007, with a median annual incidence of 0.07/100,000 children (including infants, young children, and adolescents). During the large US epidemic from 2002 through 2004, the CDC confirmed 317 cases of WNND in children less than 19 years of age; 106 of these (34%) were under 10 years of age [15, 16••]. Pediatric WNND more commonly manifests as aseptic meningitis, in contrast to the predominance of WNE observed in older individuals, but pediatric cases of WNP and WNE have also been reported [16••].

Underlying Disease Immunosuppressed recipients of transplanted organs have an increased risk of developing WNND (up to a 40-fold increase in some studies) and have more severe disease than immunocompetent individuals [24, 25]. Individuals with hematologic malignancies and impaired T-cell function are also at increased risk of WNND and poor outcome [26]. The effect of concomitant anti–B-cell therapy with rituximab has recently been reported in association with progressive and fatal neurologic disease [27]. Hypertension and cardiovascular disease have also been identified as independent risk factors for WNND [28•].

Laboratory Findings

Serology

Serologic testing of serum and cerebrospinal fluid (CSF) remains the gold standard for the diagnosis of human WNV disease [12, 20, 29]. Immunoglobulin M (IgM) antibody to WNV (usually measurable by enzyme immunoassay [EIA]) develops in 75% of WNV-infected patients by the fourth day of symptom onset; 95% of infected patients develop IgM antibody within 7 days of symptom onset. Detection of WNV IgM in CSF is diagnostic of neuroinvasive disease,

as IgM does not passively diffuse across the blood-brain barrier and is indicative of intrathecal synthesis. Because infection by related flaviviruses may elicit cross-reactive test results by EIA, a positive WNV IgM can be confirmed by WNV plaque reduction neutralization assay (CDC or state public health laboratories) for definitive diagnosis. Unlike most IgM responses, WNV IgM antibody may persist after infection for up to 12 to 16 months in the serum and as long as 7 months in the CSF [29]. Testing paired acute and convalescent sera (2–3 weeks later) to identify a fourfold rise in antibody titer or IgG avidity testing may aid in differentiating between recently acquired and previous infections with WNV [30].

PCR testing of serum or CSF is generally not useful or recommended for the diagnosis of WNV infection in immunocompetent hosts, as peak viremia occurs 3 to 4 days before symptom onset, resulting in poor sensitivity (57% in CSF and 14% in serum) [31]. Sensitivity may be higher in immunosuppressed hosts, who may lack an adequate antibody response and have prolonged viremia. The sensitivity of CSF viral culture is low, and it is not routinely used for diagnosis.

Cerebrospinal Fluid Findings

Typical CSF findings in WNND include pleocytosis (polymorphonuclear or lymphocytic predominance) with elevated protein and normal glucose levels [32]. CSF features suggestive of WNV include a prolonged polymorphonuclear predominance and the presence of abnormal-appearing reactive lymphocytes or monocytes, including plasma cell–like and Mollaret-like cells. In a recent study of 250 hospitalized patients with WNV CNS disease [32], patients with encephalitis and meningitis had similar mean CSF white blood cell counts, each approximately 225 cells/mm^3. Less than 5% of patients with either meningitis or encephalitis had fewer than 5 cells/mm^3, and fewer than 10% of patients had more than 500 cells/mm^3. The mean percentage of neutrophils was 40% to 45%. Nearly half of the encephalitis patients (but only 16% of the meningitis patients) had CSF protein levels greater than 100 mg/dL. Measurement of CSF protein biomarkers (neuronal and glial) and correlating levels to disease severity in patients with WNND infection is an emerging area of research [33].

Radiologic Findings

The incidence of acute MRI abnormalities in patients with WNND has been variable [34–36]. In one series of 39 consecutive cases of WNND (including both meningitis and encephalitis), MRI was unremarkable in all except one patient [34]. However, in each of two more recent series [35, 36], nearly 70% of patients with WNV CNS disease had abnormal MRI findings. In the first of these two studies, 12 of 17 patients had abnormal findings on MRI: 4 had abnormalities only on diffusion-weighted (DW) imaging (involving the corona radiata and internal capsule), 3 had abnormal signal intensity on fluid attenuated inversion recovery (FLAIR) or T2-weighted sequences (involving the cortical gray and white matter, cerebellum, basal ganglia, thalamus, internal capsule, pons, and midbrain), 2 had meningeal enhancement, and 3 had abnormalities involving the spinal cord, cauda equina, or nerve roots. Patients with normal MRI or only DW-image abnormalities had the best prognosis, whereas those with T2 and FLAIR abnormalities had the worst outcomes. A WNV MRI registry was established by the CDC to develop a more comprehensive picture of the imaging characteristics of WNV infection, but results have not yet been published.

Pathologic Findings

Pathologic findings in the setting of WNE are nonspecific and include microglial nodules, perivascular chronic inflammation, and variable neuronal loss, necrosis, or neuronophagia [37]. Pathologic studies in cases of fatal WNP have demonstrated that the associated signs and symptoms result from acute inflammation of anterior horn cells through direct virus-induced, immune-mediated, or excitatory mechanisms [38].

Mortality and Prognosis

Mortality

Almost all mortality due to WNV is confined to patients with WNND. Case fatality rates vary according to presentation, with higher mortality noted in patients with WNE (generally 20%, but possibly as high as 35% in elderly patients) and WNP (10%–50%), compared with less than 1% in patients with meningitis [39]. In a recent study of hospitalized patients, risk factors associated with progression from encephalitis to death were absence of pleocytosis in the CSF, renal insufficiency, requirement for mechanical ventilation, presence of myoclonus or tremors, and loss of consciousness [40].

Morbidity

To date, at least 12 studies have assessed the long-term outcomes of patients surviving WNV infection [39, 41, 42]. Most patients with WNV meningitis and no associated focal neurologic deficits make a complete recovery. Long-term outcomes and sequelae from WNE are highly variable,

including fatigue, myalgia, residual tremor, and parkinsonism. Severe neurologic deficits can be transient, lasting days or weeks, but they also have been reported to persist for months to years and in some cases are life-long.

The initial severity of encephalitic signs and symptoms is not necessarily predictive of outcome. All studies appear to substantiate a significant amount of self-reported disability following both WNF and WNND [39]. Persistent symptoms, including fatigue, muscle pain, muscle weakness, headache, and memory problems are present 6 to 18 months after illness in nearly half of patients with WNE. Younger age at infection was the only significant predictor of recovery.

Patients with WNP have the worst overall prognosis and often have significant residual weakness. Most strength recovery by WNP patients appears to occur during the first 6 to 8 months, with a subsequent plateau. Determination of the number of surviving spinal motor units using electrophysiologic techniques shows potential promise as a means of predicting eventual strength recovery. The role of physical and occupational therapies in WNP outcomes has not been formally studied [39]. Patients who required mechanical ventilation may experience dyspnea and require supplemental oxygen for years following the acute illness [39].

Neuropsychiatric Consequences

A recent analysis of WNV patients found that 31% of patients reported new-onset depression. Of these patients, 75% had Center for Epidemiologic Studies Depression scores indicative of mild to severe depression [43]. Mental status has been assessed to be poorer and cognitive complaints are more frequent following WNND than WNF [44]. In a more recent study, more than half of patients with WNND had objectively measurable neuropsychological impairment in at least two cognitive domains 1 year after symptom onset, unrelated to subjective complaints of physical or emotional distress or premorbid intellectual abilities [45].

Virus and Host Determinants of WNND Pathogenesis

Virus Determinants

Genome sequencing and reverse genetic approaches have provided insight into the virulence of North American WNV strains [46••]. The basis for the emergence of the large-scale North American epidemic has been proposed to be the introduction of a single amino acid substitution in the WNV NS3 helicase, encoding increased blood virus levels and higher fatality rates in the American crow species [47]. Molecular epidemiologic studies indicate that two genetic variants emerged in 2002, with the major variant (WNV 2002) dominating circulation in most parts of the United States. This major variant has a single amino-acid change in the envelope protein, conferring greater capacity for viral replication in mosquitoes and higher transmissibility to birds, thus facilitating rapid geographic expansion [48].

Murine models have demonstrated that US strains are highly neurovirulent and neuroinvasive in rodents. Comparative sequencing of nonneuroinvasive and neuroinvasive strains has suggested that glycosylation of the envelope protein is a major determinant of the neuroinvasive phenotype [49]. Additionally, mutation of the WNV NS4B nonstructural protein confers attenuation of the neuroinvasive and neurovirulent phenotype in mice [50].

Host Factors

Host Immunity

Mouse models have demonstrated the importance of innate (TLR, IFNα/β), humoral (B cells and antibody), and cellular (CD8+ T cells, CD4+ T-regulatory cells) immunity in controlling WNV infection [46••, 51]. Humoral immunity limits dissemination: the envelope E glycoprotein is the major viral protein eliciting neutralizing antibodies, and thus is the main target for vaccine development [46••]. The maturation state of the virion and nonneutralizing protective antibodies directed against NS1 nonstructural glycoprotein are also likely to be important for protection in vivo [46••]. Cellular immunity is required for clearance of neurovirulent strains of WNV; impaired T-cell function is a risk for neuroinvasive disease and poor outcome [46••]. A recent study demonstrated an increased number of terminally differentiated, memory phenotype T cells in patients suffering from WNND; this was the first study to associate disease outcome with a particular CD8 T-cell phenotype [52]. Recent studies in mice and humans suggest that higher levels of T-regulatory cells following infection protect against severe WNV infection in immunocompetent animals and humans [53]. The role of cytokines has also been of recent interest in the pathogenesis of neuroinvasive disease: Suppressors of cytokine signaling (SOCS) may play a role in enhancing the ability of WNV to spread and cause disease [54]. WNV-induced, neuron-derived proinflammatory cytokines may also contribute to neurotoxicity [55].

Host Genetics

Two human genes have been identified that confer increased susceptibility to WNV infection: the chemokine receptor CCR5, and the 2′ 5′ oligoadenylate synthetase

(*OAS1*) gene, a member of an IFN-regulated gene family involved in degradation of viral RNA [46••]. Approximately 1% of the general US population, and up to 8% of patients with symptomatic or lethal WNV infection, are homozygous for the *CCR5Δ32* allele, suggesting the function of CCR5 function as a potentially important host factor for resistance to neuroinvasive WNV infection [56]. In contrast, recent data in humans suggest that although *OAS1* is a genetic risk factor for the acquisition of infection, it is not a risk factor for disease severity [57].

Therapeutics

At present, there is no specific therapy with proven efficacy for the treatment of WNV infection. Current treatment of WNND is largely supportive. In transplant patients with presumed WNE, early withdrawal of immunosuppression is recommended [24, 25]. The efficacy of corticosteroids for the treatment of WNV has not been studied.

Investigational Agents

Ribavirin

Ribavirin appears to have limited clinical efficacy and seems to produce detrimental effects in rodent models, despite demonstrated efficacy against WNV in vitro [58••]. Increased mortality was seen in patients treated with ribavirin during an Israeli WNV outbreak [59].

Mycophenolic Acid

Mycophenolic acid (MPA) limits WNV infection in vitro by limiting viral RNA replication, and it blocked WNV infection efficiently in vitro. However, increased mortality was observed in mice following infection, likely because of immunosuppressive effects [58••].

Interferon

Interferon (IFN)-α2b inhibits growth of WNV in vitro and can protect BALB/c mice and golden hamsters from WNV-induced disease, although its efficacy is greatly diminished when treatments are delayed beyond 4 to 6 h before viral challenge [60]. IFN-α/β-receptor knockout mice had 100% mortality following WNV challenge, whereas pretreatment of rodents with IFN-α resulted in decreased WNV viral loads and mortality [61]. The efficacy of IFN treatment in humans is still unclear, as interferon has been studied only in a nonblinded, non–placebo-controlled clinical trial; a randomized, placebo-controlled clinical trial is still in progress [62].

Immunoglobulin

Passive transfer of WNV-specific antibodies or immunoglobulin can protect mice and hamsters against lethal WNV infection in experimental models of disease [63, 64]. Passive transfer has been shown to improve clinical outcome even after WNV has disseminated to CNS in mice. Uncontrolled clinical reports describe a beneficial effect in small numbers of patients given the Israeli human intravenous immunoglobulin preparation Omr-IgG-am™, which contains high titers of neutralizing antibody to WNV (reviewed in [58••]). A multicenter, randomized, placebo-controlled phase I/II trial sponsored by the National Institutes of Health to test the effectiveness of this preparation in humans with WNV disease began in 2003, but results have not yet been published.

Monoclonal Antibodies

The humanized monoclonal antibody E16, which targets the WNV envelope protein, has shown therapeutic efficacy in mice, reducing paralysis and mortality even when administered as a single dose 5 days after WNV infection [65–69]. An equally effective plant-derived humanized anti-WNV monoclonal E16 antibody, which can be rapidly scaled up for commercial production, has also been developed [70]. A phase I/II randomized, blinded clinical trial to evaluate monoclonal E16 antibody against severe WNV infection has been completed but results are not yet available (http://clinicaltrials.gov/ct2/show/NCT00515385).

Antisense Oligomers

A proprietary antisense oligomer construct (AVI-4020, AVI BioPharma), which inhibits viral replication [71], was found to be safe in a small pilot phase I human clinical trial. A more extensive randomized, double-blinded placebo-controlled trial to assess safety, tolerability, pharmacokinetics, and potential efficacy was terminated because of limited enrollment.

RNA Interference

Two studies have shown that administration of siRNA in mice reduces WNV load and provides partial protection against lethal challenge [72]. RNA interference (RNAi) constructs have also been studied in human cells in vitro but have not shown efficacy. Further developments may require enhanced delivery systems to allow siRNA to cross intracellular membranes and inhibit virus replication [58••].

Other Compounds

Mice challenged with WNV who were administered E protein inhibitor peptides showed reduced viremia and

lethality [73]. Imino sugar derivatives that prevent processing growth of WNV have also been recently developed for use in vitro and in vivo [74]. High-throughput screening of thousands of compounds using small-molecule libraries has identified classes of compounds that inhibit WNV by attenuating translation, protease activity, and replication. These compounds are now just starting to be evaluated in animal models to assess therapeutic potential [58••].

Conclusions

WNV remains the leading cause of epidemic meningoencephalitis of humans in North America. Although fewer than 1% of infected individuals develop WNND (manifesting as meningitis, encephalitis, or poliomyelitis), mortality is high, and neurologic and neuropsychiatric sequelae among survivors are severe and often permanent. In the 12 years since the first emergence of WNV in the Western Hemisphere, much progress has been made with regard to understanding virus and host determinants of pathogenesis, the spectrum of clinical manifestations, and risk factors for severe and neuroinvasive disease. Nevertheless, effective specific therapies are still lacking and remain an area of active research.

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- •• Of major importance

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