Fatal Hemorrhagic Fever Caused by West Nile Virus in the United States

Christopher D. Paddock,1 William L. Nicholson,2 Julu Bhatnagar,1 Cynthia S. Goldsmith,1 Patricia W. Greer,1 Edward B. Hayes,3 Joseph A. Risko,4 Corey Henderson,4 Carina G. Blackmore,7 Robert S. Lanciotti,3 Grant L. Campbell,7 and Sherif R. Zaki1

1Infectious Disease Pathology Activity and 2Viral and Rickettsial Zoonoses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 3Arboviral Diseases Branch, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado; 4Florida Hospital Waterman, Tavares, and 5Florida Department of Health, Tallahassee

Background. Most West Nile virus (WNV) infections in humans are asymptomatic; severe disease occurs in relatively few patients and typically manifests as encephalitis, meningitis, or acute flaccid paralysis. A few cases of life-threatening disease with diffuse hemorrhagic manifestations have been reported in Africa; however, this clinical presentation has not been documented for any of the >16,700 cases of WNV disease reported in the United States during 1999–2004. We describe a case of fulminant WNV infection in a 59-year-old Florida man who died following a brief illness that resembled hemorrhagic disease caused by Rickettsia rickettsii, dengue virus or yellow fever virus.

Methods. Traditional and contemporary diagnostic assays, including culture isolation, electron microscopic examination, reverse-transcriptase polymerase chain reaction amplification, and immunohistochemical stains, were used to confirm systemic WNV infection in the patient.

Results. WNV was isolated in a cell culture from a skin biopsy specimen obtained from the patient shortly prior to death. Electron microscopic examination identified the isolate as a flavivirus, and reverse-transcriptase polymerase chain reaction amplified specific WNV sequences from the isolate and patient tissue. Quantitative polymerase chain reaction identified approximately 1 × 107 viral copies/mL in the patient’s serum. WNV antigens were detected by immunohistochemical stains in intravascular mononuclear cells and endothelium in skin, lung, liver, kidney, spleen, bone marrow, and central nervous system; no viral antigens were identified in neurons or glial cells of the central nervous system.

Conclusions. Although hemorrhagic disease is a rare manifestation of WNV infection, the findings provided by this report may offer new insights regarding the clinical spectrum and pathogenesis of WNV disease in humans.

West Nile virus (WNV), the cause of West Nile fever and West Nile encephalomyelitis, is a flavivirus antigenically similar to Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus [1]. WNV also shares some antigenic determinants with other arthropod-borne flaviviruses that cause hemorrhagic fevers, including dengue virus (DENV), yellow fever virus (YFV), Kyasanur Forest disease virus, and Omsk hemorrhagic fever virus. Most WNV infections in humans are asymptomatic; severe disease occurs in relatively few patients and most frequently manifests as encephalitis, meningitis, or acute flaccid paralysis [2–7]. Rare cases of severe or fatal hemorrhagic fever–like disease with coagulopathy, fulminant hepatitis, and spontaneous hemorrhaging have been reported in the Central African Republic [8] and South Africa [9]. During 1999–2004, a total of 16,706 cases of WNV disease, including 9268 cases of West Nile fever, 7096 cases of neuroinvasive disease, and 666 deaths, were reported in the United States [10]; however, hemorrhagic fever caused by WNV has not been documented previously in the Western Hemisphere.

CASE REPORT

A 59-year-old, previously healthy man presented to an emergency department in central Florida in July 2003
with severe hypotension, metabolic acidosis, and acute renal failure. The patient had returned 2 days earlier from a 4-day boating trip across southern Florida that included travel across Lake Okeechobee and through various inland waterways. During this trip, he received numerous mosquito bites, and on the last day, he reported fatigue, malaise, and weakness. One day later he developed chills, nausea, vomiting, and dark urine, and loose, blood-streaked stools. The patient was a nursery owner and had returned 12 days before hospital admission from a business trip to a farm near San José, Costa Rica; he had traveled there frequently during the previous 20 years. His medical history included non–insulin-dependent diabetes mellitus, hypertriglyceridemia, and hypertension.

Physical examination revealed an alert and anxious man with cool, pale skin. His temperature was 35.6°C, his pulse was 126 beats per min, his respiratory rate was 24 breaths per min, and his blood pressure was 94/59 mm Hg. Small petechiae were present on his lower extremities and upper arms. Diffuse ecchymoses were present on his abdomen and upper thighs. His WBC count was 7.3 × 10^3 cells/mm^3 (25% metamyelocytes, 45% bands, 24% segmented neutrophils, 4% lymphocytes, and 2% monocytes), his hemoglobin level was 17.0 g/dL, his hematocrit level was 50.3, and his platelet count was 84 × 10^4 platelets/mm^3. His fibrin D-dimer concentration was elevated at >2.00 µg/dL, his prothrombin time was increased at 22.2 s, and his activated partial thromboplastin time was increased at 46.8 sec. Other laboratory values included a low bicarbonate level (18 mmol/L); elevated levels of blood urea nitrogen (25 mg/dL), creatinine (2.9 mg/dL), lactate dehydrogenase (515 U/L), aspartate aminotransferase (146 U/L), alanine aminotransferase (87 U/L), alkaline phosphatase (167 U/L), and total bilirubin (3.9 mg/dL); a normal total protein level (5.6 g/dL) with a low level of albumin (2.4 g/dL); a normal lactic acid level (9.3 mmol/L), and a normal creatine kinase (MB isoenzyme) level (5.9 µg/L). His urine contained 5–10 leukocytes and 5–10 RBCs per high power field.

The patient was admitted to an intensive care unit with a diagnosis of septic shock and was given pressor support, fluid resuscitation, sodium bicarbonate, and rocephin. Routine blood cultures showed no growth of bacterial pathogens. Because of concerns about potentially fastidious or noncultivable bacteria, the patient’s antibiotic coverage was expanded to include doxycycline, cefepime, vancomycin, and gatifloxacin. He developed diffuse palpable purpura of the back and lower extremities. A skin-punch biopsy specimen showed dermal hemorrhage and fibrin thrombi. Tests for hepatitis B virus surface antigen and for antibodies reactive with hepatitis A and C viruses, Rickettsia rickettsii, Rickettsia typhi, Leptospira species, and Coxiella burnetii were negative. His serum complement C3 level was slightly decreased at 83 mg/dL, and the C4 level was markedly decreased at <8 mg/dL. The patient’s renal insufficiency worsened, and his blood urea nitrogen and creatinine levels rose to 47 mg/dL and 5.6 mg/dL, respectively. He remained severely hypotensive and acidic and died ∼24 h after admission. Serum and skin biopsy specimens were sent to the Centers for Disease Control and Prevention for diagnostic evaluation.

METHODS

Serology. A serum specimen was tested for IgG antibodies to R. rickettsii, R. typhi, Ehrlichia chaffeensis, and Anaplasma phagocytophilum using an indirect immunofluorescence antibody assay with a fluorescein isothiocyanate-conjugated goat anti–human IgG (Kirkegaard and Perry Laboratories) at a dilution of 1:150. The same specimen was subsequently evaluated for IgG and IgM antibodies to WNV, St. Louis encephalitis virus, and DENV using EIAs and plaque-reduction neutralizing tests [11].

Histopathological and immunohistochemical examination. A 4-mm punch biopsy specimen was obtained from a purpuric skin lesion and bisected; 1 piece was saved for cell culture isolation and the other was placed in 10% buffered formalin for histologic evaluation. Sections (3 µm) cut from formalin-fixed, paraffin-embedded skin were stained with hematoxylin-eosin and tested for spotted fever group rickettsiae, Neisseria meningitidis, and various flaviviruses using an immunoalkaline phosphatase technique [12–15]. The primary antibodies included rabbit anti–R. rickettsii antibody (at a dilution of 1:500); horse anti–N. meningitidis serogroup Y antibody (at a dilution of 1:500); polyclonal mouse anti–Japanese encephalitis virus ascitic fluid (broadly reactive with various flaviviruses, including Japanese encephalitis virus, St. Louis encephalitis virus, WNV, DENV, and YFV, at a dilution of 1:800); polyclonal mouse anti–YFV ascitic fluid (specific for YFV, at a dilution of 1:1000), a polyclonal mouse anti–DENV (serotype 2) ascitic fluid (broadly reactive with various flaviviruses, including DENV serotypes 1–4 and WNV, at a dilution of 1:1000); and pooled monoclonal anti-WNV antibodies (clones 5H10 and 3A3, specifically reactive with WNV, each at a dilution of 1: 400).

Cell culture. A piece of the skin biopsy specimen was triturated in RPMI 1640 medium (Gibco Invitrogen). The homogenate was transferred to Vero E6 cells in a 25-cm² polystyrene cell culture flask and overlaid with 7 mL of cell culture medium containing 10 U/mL of penicillin G, 10 µg/mL of streptomycin sulfate 1 µg/mL of amphotericin B and incubated at 37°C in a 5% CO₂-enriched atmosphere. After 2 days, the cell culture medium was replaced with antibiotic-free medium. This medium was replaced weekly, and cell culture supernatant was passed to fresh cells when cytopathic changes of the monolayer were observed; cell cultures were subsequently evaluated using electron microscopy, immunohistochemical stains, and molecular assays.
**Electron microscopy.** Infected Vero E6 cells were fixed at room temperature with 2.5% glutaraldehyde in 0.1 mol/L phosphate buffer, scraped from the flask, and collected by centrifugation. The pellet was fixed for an additional hour, postfixed for 30 min with buffered 1% osmium tetroxide, dehydrated in a series of graded ethanol concentrations and propylene oxide, and embedded in an Epox substitute–Araldite mixture.

**Molecular analyses.** DNA was extracted from a portion of triturated skin used as primary inoculum for cell culture by a QIAamp DNA Mini Kit (Qiagen Sciences). The extract was evaluated using a nested PCR assay targeting the 17-kDa rickettsial common antigen (htr) gene [12]. RNA was extracted from sections (10 μm) cut from formalin-fixed, paraffin-embedded skin using the Paraffin Block RNA Isolation Kit (Ambion), and from formalin-fixed, infected Vero E6 cells using the RNeasy Mini Kit (Qiagen Sciences). RT-PCR assays were performed with the One-step Access RT-PCR Kit (Promega) using published primers for WNV and DENV (table 1). All samples were tested using a flavivirus-specific, hemi-nested RT-PCR assay targeting the NS5 gene [16, 17] and WNV-specific, single-stage or nested RT-PCR assays targeting the capsid and premembrane [18, 19], envelope [20], and NS1 genes [18], and the 3′ untranslated region [18]. Two RT-PCR assays were used to evaluate for the capsid and premembrane genes of DENV [21, 22]. Amplicons of the appropriate size were identified by electrophoresis in a 1.8% agarose gel. PCR products were extracted from the gel using the QIAquick Gel Extraction Kit (Qiagen Sciences) and directly sequenced on a CEQ 2000 XL sequencer (Beckman Coulter). Search for homologies to known sequences was done using the nucleotide database of the Basic Local Alignment Search Tool [23]. The nucleotide sequences were compared and aligned with published WNV sequences using Clustal W [24] and the GCG package. Nucleic acid extracted from ∼200 μL of serum obtained on day 3 of the patient’s illness was tested for WNV and DENV nucleic acids by a quantitative real-time RT-PCR assay using TaqMan [18, 22].

**RESULTS**

A serum specimen obtained on day 3 of the patient’s illness showed no IgG antibodies to *R. rickettsii*, *R. typhi*, *E. chaffeensis*, or *A. phagocytophilum* using immunofluorescence antibody assays. No IgG antibodies to WNV, DENV serotypes 1–4, or St. Louis encephalitis virus were detected in this specimen by EIA. Results of the IgM-capture EIA for WNV were noninterpretable. Neutralizing antibody titers were 160 to DENV serotype 2, 40 to DENV serotype 4, 10 to WNV, and 10 to St. Louis encephalitis virus.

Histopathological evaluation of the skin biopsy specimen showed hemorrhage in the superficial dermis (figure 1A) and mild perivascular infiltrates of lymphocytes and macrophages in the superficial and deep dermis. Small vessels contained multiple occlusive fibrin thrombi (figure 1B) and showed mural damage and extravasation of erythrocytes. Immunohistochem-

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Table 1. PCR primers used and gene targets evaluated in molecular analyses of cutaneous tissue, serum, and a cell culture isolate obtained from a patient with fatal West Nile virus disease.

<table>
<thead>
<tr>
<th>Gene target</th>
<th>Primer (sequence)</th>
<th>Product size, in bp</th>
<th>Reference</th>
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<tr>
<td>Pan-flavivirus NS5 gene</td>
<td>MA-F (CAT GAT GGG RAA RAG RGA RRA G)</td>
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<td>[16]</td>
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<td>Pan-flavivirus NS5 gene</td>
<td>cFD2-R (GTG TCC CAG CCG GGC GTG TCA TCA GC)</td>
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<td>Pan-flavivirus NS5 gene</td>
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<td>WN233 (TTG TGT TGG CTC TCT TGG CTT TCT T)</td>
<td>408</td>
<td>[18]</td>
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<tr>
<td>WNV capsid and premembrane genes</td>
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<tr>
<td>WNV capsid and premembrane genes</td>
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<td>[19]</td>
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<td>WNV 3′ untranslated region</td>
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<td>103</td>
<td>[18]</td>
</tr>
<tr>
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<td>WN 3NC-R (CTA GGC CCG CGT GGG)</td>
<td>...</td>
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<tr>
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<td>248</td>
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<tr>
<td>DENV capsid gene</td>
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* Primer used in a hemi-nested assay with cFD2-R.
Figure 1. Cutaneous pathology of a tissue specimen of a patient with fatal West Nile virus (WNV) infection, as well as immunohistochemical localization of WNV and ultrastructural features of a WNV isolate. 

A, Extravasation of erythrocytes in the superficial dermis (hematoxylin-eosin stain; original magnification, ×50). 
B, Fibrin thrombi in small dermal vessels (hematoxylin-eosin stain; original magnification, ×100). 
C and D, Immunohistochemical localization of WNV antigens (red) in perivascular mononuclear inflammatory cells and free within the lumen of small dermal vessels (C, immunoalkaline phosphatase with naphthol fast-red and hematoxylin counterstain, hyperimmune mouse anti–Japanese encephalitis virus ascitic fluid [original magnification, ×100]; D, pooled monoclonal anti-WNV antibodies, clones 5H10 and 3A3 [original magnification, ×100]). 
E, WNV isolated from skin in Vero E6 cells. Spherical particles with a dense core and tightly bound envelope have accumulated in the extracellular space (uranyl acetate and lead citrate stain; the black bar equals 1 μm).
Figure 2. Tissue pathology of tissue specimens of a patient with fatal West Nile virus (WNV) infection and immunohistochemical localization of WNV in the patient’s liver, spleen, kidney, and lung. A, Focus of hepatocyte necrosis and inflammatory cell infiltrates in the liver (hematoxylin-eosin stain; original magnification, ×50). B, WNV antigens in Kupffer cells (original magnification, ×100). C, Fibrin thrombi in splenic sinusoids (hematoxylin-eosin stain; original magnification, ×100). D, WNV antigens in vascular endothelium and mononuclear inflammatory cells in the spleen (original magnification, ×158). E, WNV antigens in glomerular capillaries (original magnification, ×158). F, Intravascular staining of WNV antigens in mononuclear cells and the endothelium (G) of pulmonary vessels (original magnification, ×158). Immunohistochemical phosphatase with naphthol fast-red and hematoxylin counterstain, hyperimmune mouse anti–Japanese encephalitis virus ascitic fluid (B, D, E, and F) or pooled monoclonal anti-WNV antibodies, clones 5H10 and 3A3 (G).

Immunohistochemical assays for R. rickettsii and N. meningitidis were negative. Immunohistochemical assays for Japanese encephalitis virus and DENV, each broadly reactive with various flaviviruses, and WNV-specific immunohistochemical tests demonstrated viral antigens in the cytoplasm of vascular endothelium (figure 1C) and perivascular mononuclear inflammatory cells (figure 1D). Immunohistochemical tests for WNV also demonstrated fine, intravascular, extracellular viral antigens (figure 1D). No staining of viral antigens was identified using the immunohistochemical assay for YFV.

No detectable rickettsial DNA was amplified from the skin biopsy extract by using the 17 kDa antigen gene PCR assay.
Figure 3. Immunohistochemical localization of West Nile virus (WNV) in CNS tissue specimens of a patient with fatal WNV disease. A, WNV antigens in endothelium and intravascular mononuclear cells in a small vessel in the midbrain. B, Intracellular staining of WNV antigens in mononuclear cells in vessels of the basal ganglia. C and D, Intracellular staining of WNV antigens in mononuclear cells in the choroid plexus. (Immunoalkaline phosphatase with naphthol fast-red and hematoxylin counterstain; A and C, pooled monoclonal anti-WNV antibodies, clones 5H10 and 3A3; B and D, hyperimmune mouse anti–Japanese encephalitis virus ascitic fluid; original magnifications, ×158).

No DENV sequences were amplified from RNA extracts of the formalin-fixed, paraffin-embedded skin biopsy specimen or cell culture isolate; however, segments of several WNV gene sequences were amplified from these same extracts, including 250–base pair (bp) and 220-bp segments of the NS5 gene, 408-bp and 104-bp segments of the capsid and premembrane genes, a 103-bp segment of 3′ untranslated region sequence, a 148-bp segment of the NS1 gene, and 445-bp and 248-bp segments of the envelope gene. Sequence analyses of all amplicons showed 98%–100% homology with the corresponding sequences of WNV. A serum sample obtained on the day of the patient’s death was tested by a TaqMan RT-PCR assay for DENV serotypes 1–4 and WNV. No DENV nucleic acid was detected; however, the specimen was positive for WNV at ∼1 × 10^7 copies/mL by quantitative PCR.

Lysis of the Vero cell monolayer was observed 11 days after inoculation of the skin biopsy specimen. Electron microscopic examination demonstrated spherical, dense-core, viral particles ∼45 nm in diameter, in the rough endoplasmic reticulum and along the cell membrane. Smooth membrane vesicles, a characteristic feature of flaviviruses, were also identified in the rough endoplasmic reticulum (figure 1E). The isolate was confirmed as WNV by immunohistochemical staining using monoclonal antibodies and by PCR and sequencing of several flavivirus genes.

Several months after the diagnosis was established from the skin biopsy specimen, an epidemiologic investigation revealed that a private autopsy had been performed at the family’s request, and these tissues were made available to the Centers for Disease Control and Prevention for histopathological and immunohistochemical evaluation. The liver showed scattered hepatocyte necrosis, and occasional foci of more extensive hepatocellular necrosis accompanied by neutrophilic infiltrates, microvesicular steatosis, and erythropagocytosis by Kupffer cells (figure 2A). Other findings included multifocal intraalveolar hemorrhage and edema in the lungs; fibrin thrombi in the small vessels of the kidney, spleen, lung, and bone marrow (figure 2C); lymphocyte depletion of the spleen; and scattered mixed inflammatory cell infiltrates in the adrenal glands. The heart, pancreas, and multiple areas of the CNS, including leptomeninges, cerebral cortex, basal ganglia, hippocampus, midbrain, medulla, and cerebellum, showed no conspicuous inflammatory cell infiltrates. Immunohistochemical staining revealed disseminated WNV antigens in macrophages; intravas-
cular mononuclear inflammatory cells; or vascular endothelium in the skin, stomach, lung, liver, kidney, spleen, bone marrow (figure 2B and 2D–2G) and in various areas of the CNS (figure 3A–3D). No staining of neurons or glial cells was identified in any region of the CNS.

**DISCUSSION**

The diagnosis of WNV infection in this patient was confirmed by isolating WNV from a skin biopsy specimen, staining for WNV antigens in various tissues, and amplifying several regions of the WNV genome from the viral isolate and patient tissue and serum. The clinical and epidemiologic presentation of this patient directed the initial laboratory investigation toward other hemorrhagic fever syndromes, including Rocky Mountain spotted fever, meningococcemia, and dengue. The history of rash, multiorgan failure, and recent arthropod bites suggested Rocky Mountain spotted fever, prompting biopsy of the rash and evaluation of the specimen by immunohistochemical examination and cell culture for spotted fever group rickettsiae.

The confirmation of a flavivirus by culture and electron microscopy initially focused attention to dengue, particularly because the patient had travelled repeatedly to a dengue-endemic country, most recently within 2 weeks of disease onset. In addition, clinical and laboratory manifestations of this patient’s disease were remarkably consistent with those observed in hemorrhagic fevers caused by other viscerotropic flaviruses, including YFV and DENV. Although the patient had neutralizing antibodies to DENV serotypes 2 and 4, no anti-DENV IgM antibody was detected, nor was DENV detected in clinical specimens by using cell culture or RT-PCR, suggesting that the patient’s anti-DENV antibodies were the result of a remote DENV infection. It is not surprising that neutralizing antibodies to WNV were low in this patient, because the serum sample was collected only 3 days after onset of illness and specific neutralizing antibodies to WNV generally do not develop until the second or third week following symptom onset [25, 26].

Focal or diffuse hemorrhagic manifestations of WNV infection have been documented rarely [3, 8, 9]. WNV was isolated from liver or serum specimens of 4 (8%) of 51 patients with acute febrile hepatitis in the Central African Republic during 1980–1984; bleeding diatheses occurred in 2 patients, including 1 who died [8]. WNV was isolated from a patient with coagulopathy, hemoglobinuria, and acute renal failure in South Africa during 1989 [9]. In the United States, hemorrhagic pancreatitis was described in 1 patient with WNV infection during the 1999 WNV outbreak in New York [3].

Following inoculation in a susceptible human host, WNV spreads to regional lymph nodes, spleen, and other reticuloendothelial tissues, and replicates to produce a high-titer viremia before invading the CNS [27, 28]. WNV is tropic for neurons and microglia in patients with fatal encephalitis [14]; however, the cellular targets of peripheral WNV replication have not been characterized. Studies of other flaviviruses, including DENV, have identified viral replication in macrophages and monocytes [29]. We found antigens of WNV in endothelium and intravascular and perivascular mononuclear inflammatory cells, presumably monocytes and macrophages, providing some evidence that WNV replicates in ≥1 of these cell types.

WNV replicates to high titers in mouse brain endothelial cells in vitro [30] and may localize and proliferate in blood vessel tissues of suckling mice [31]. Recent studies of mice infected with WNV indicate that viral antigens can also localize in hepatocytes and hepatic capillaries [32]. Localization of WNV to the vascular endothelium is not definitive evidence of active viral replication in endothelial cells and could represent pinocytosis of viral antigens; however, some manifestations of WNV disease in humans, including retinal vasculitis [33] and frequent exanthems (described for approximately 10%–15% of patients with invasive CNS disease and 50%–60% of patients with West Nile fever [2, 6, 34–36]), suggest that microvascular damage, caused directly or indirectly by WNV infection, occurs in some clinical situations. Hemorrhagic lesions of the lung, spleen, pancreas, heart, gastrointestinal tract, and CNS have also been described in fatal avian WNV infections. However, macrophages, monocytes, Kupffer cells, and reticuloendothelial cells of the spleen appear to be the principal targets of viral infection in birds, and antigens of WNV have been documented only rarely in vascular smooth muscle or the endothelium of a few avian species [37, 38].

The pathophysiologic mechanism responsible for the rapid and severe clinical course in this patient is unknown. All North American isolates of WNV show high nucleotide and amino acid sequence homologies [39], suggesting that major differences in virulence among strains infecting patients in the United States are unlikely. However, viremias recorded for U.S. patients with WNV infection are considerably lower [10, 40] than the viremia identified for the patient described in this article, and it is possible that ≥1 genetic factors peculiar to this patient influenced development of the remarkably high viral load and systemic clinical manifestations that resulted in his death. A recent investigation of 2 patient cohorts with laboratory-confirmed WNV disease demonstrated that a defective allele for the monocyte and T lymphocyte chemokine receptor CCR5 (CCR5Δ32) is a genetic risk factor for symptomatic WNV infection, and that CCR5Δ32-homozygous individuals who lack CCR5 function may be at greater risk for fatal WNV disease, compared with WNV-infected persons among the general population [41].

Other studies have identified a single nucleotide polymorphism in a 2′-5′-oligoadenylate synthetase (OAS)-like gene (OASL1) that occurs at a significantly higher frequency in patients with severe WNV disease than in matched control sub-
jects [42]. It is postulated that RNA transcripts of this gene undergo increased splicing and result in a mutant OAS1 isoform that is similar to a mutant 1b isoform of the OAS5 gene in mice. Susceptibility of Mus species to flaviviruses has been mapped to Oas1b [43, 44]. Inbred strains of laboratory mice that express the mutant Oas1b gene typically develop severe meningoencephalitis and die following inoculation of WNV and virus replicates to high titers in splenic and peritoneal macrophage cultures prepared from susceptible mice. In contrast, wild Mus species express the wild-type allele of Oas1b, and are innately resistant to WNV and other flaviviruses. WNV replication is 200 times lower, or altogether inhibited, in macrophages harvested from resistant strains found in mice [45].

The presence of anti-DENV antibodies in this patient suggests that he had been infected previously with at least 1 DENV serotype. Pre-existing DENV antibody is considered to be a risk factor for the development of dengue hemorrhagic fever upon subsequent exposure to a heterologous DENV serotype. It has not been determined whether previous flavivirus infection poses a risk or serves as a preventive factor in the development of severe WNV disease [46–48]. Although it is clear that anti-DENV antibodies did not protect this patient from fatal infection with WNV, it is unknown whether these antibodies contributed to the severity of his illness.

Various systemic manifestations of WNV disease, including hepatitis, pancreatitis, and myocarditis, have been reported in patients from Africa, Israel, and Russia [8, 9, 49–51], and more recently, in a few patients from the United States [52–54]. This report adds to earlier data that document WNV involvement of multiple organs beyond the CNS. Why some individuals develop severe disease following WNV infection and others have milder illness or remain asymptomatic remains an important question awaiting further study.

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Potential conflicts of interest. All authors: no conflicts.

References


