West Nile Virus (WNV) is a mosquito-borne flavivirus, which has been known to cause human infection in Africa, the Middle East, and southwestern Asia. It has also been isolated in Australia and sporadically in Europe but never in the Americas. Clinical features include acute fever, severe myalgias, headache, conjunctivitis, lymphadenopathy, and a roseolar rash. Rarely is encephalitis or meningitis seen. During the month of August 1999, a cluster of 5 patients with fever, confusion, and weakness were admitted to the intensive care unit of the same hospital in New York City. Ultimately 4 of the 5 developed flaccid paralysis and required ventilatory support. Three patients with less-severe cases presented shortly thereafter. With the assistance of the New York City and New York State health departments and the Centers for Disease Control and Prevention, these were documented as the first cases of WNV infection on this continent.

West Nile virus (WNV) is a member of the family Flaviviridae. It was first isolated in 1937 from the blood of a febrile Ugandan woman [1]. WNV is found throughout Africa and the Middle East and in parts of Europe, Russia, India, and Indonesia. In areas of endemicity, illness is often asymptomatic. Transmission principally involves the *Culex* species mosquitoes and wild birds as the hosts. Humans, horses, and domestic animals are usually incidental hosts [2]. In the Nile Delta region of Egypt, where WNV is endemic, seroprevalence ranges from 6% in schoolchildren to 40% in young adults [3]. Introduction of this virus into areas without immunity can cause epidemics. This is exactly what occurred during August 1999 in New York City (NYC). We describe here the first 5 patients admitted to our intensive care unit (ICU) suffering from severe neurological infection caused by WNV and 3 subsequently identified patients with less-severe infection (2 with meningitis and 1 with encephalitis).

Case Reports

**Patient 1.** On 12 August 1999, a 60-year-old man was admitted to the hospital with complaints of fever, weakness, and nausea for 3 days. Physical examination revealed a well-tanned man with a maximum temperature of 39.7°C but with no other remarkable symptoms. A chest radiograph suggested bibasilar infiltrates and the patient was placed on iv erythromycin and ceftriaxone. On day 4, he was found to be confused, with proximal muscle weakness, decreased deep tendon reflexes, and respiratory difficulty. There also was urinary retention. He was placed on bilevel positive airway pressure ventilatory assistance. A lumbar puncture (LP) and CT scan of the head were done (table 1). The medications were changed to iv ceftriaxone and acyclovir. Electromyogram/nerve conduction velocities studies (EMG/NCV) showed axonal type polyneuropathy. Guillain-Barre syndrome (GBS) was thought to be a possible diagnosis, so plasmapheresis was initiated. Over the next several weeks, his muscle weakness and mentation improved. Bladder catheterization, however, was still required. He was subsequently transferred to another institution for rehabilitation for 1 month. Five months after his primary infection, he walks with a quad cane, has left side weakness, and has episodes of recent memory loss.

**Patient 2.** On 15 August, an 80-year-old man with a history of mild congestive heart failure was admitted with complaints of fever, headache, weakness, and diarrhea for 1 week. On the day of admission, his wife found him unresponsive, and paramedics were called. After tracheal intubation, he developed ventricular tachycardia and asystole. He was successfully resuscitated. At the hospital, his temperature was 40°C, and his exam revealed a sun-tanned, well-built man without any abnormalities except that he was obtunded and on a ventilator. He was given iv ceftriaxone and clindamycin for possible aspiration pneumonia. A head CT and LP were performed (table
Medical complications that developed included an anterior wall myocardial infarction requiring dobutamine, hypotension requiring vasopressor agents (dopamine and norepinephrine), ischemic hepatothaply, renal insufficiency, and disseminated intravascular coagulation. On day 3, the amylase was 672 IU/L. Over the next few days he became flaccid; an EMG/NCV showed motor axonopathy without sensory involvement. After 3 weeks, life support was removed, and the patient died. Autopsy revealed encephalitis. Microscopic exam showed microglial nodules scattered in the gray and white matter of the cerebrum. Scanty mononuclear inflammatory infiltrate was present in the leptomeninges. The general autopsy was limited at the family’s request and revealed only hemorrhagic pancreatitis.

**Patient 3.** On 18 August, a 75-year-old man with a history of prostate cancer presented with a sudden change in mental status, fever, and urinary incontinence. On admission, his temperature was 39.5°C. Neurologically he was oriented to person and place, with neck rigidity and diffuse tremors in both upper and lower extremities. Deep tendon reflexes were brisk. A CT scan of the head and LP were performed (table 1). He was placed on iv ampicillin, ceftriaxone, and acyclovir. On day 2, he required mechanical ventilation. Subsequently he developed diffuse muscle weakness and decreased deep tendon reflexes. EMG/NCV showed diffuse polyneuropathy with axonal involvement. After 3 weeks, he died. Autopsy revealed encephalitis. On microscopic sections, microglial nodules were present in the medulla, cerebellum, and thalamus. Rare lesions were also present in the cerebrum, particularly the hippocampus. Perivascular inflammation was seen in the medulla. There was no leptomeningeal inflammation. In some cranial nerve roots of the medulla, there was focal mononuclear inflammation. The remainder of the autopsy showed no histologic evidence of pancreatitis, myocarditis, or hepatitis.

**Patient 4.** On 20 August, an 87-year-old woman with a history of breast and colon cancer was admitted with complaints of 1 week of headache, loose stools, fever, and weakness. In the hospital, she appeared dehydrated but alert, with a normal physical exam except for some mild dysarthria. On day 6 the patient became obtunded, with diffuse muscle weakness, and was intubated. Her temperature rose to 38.7°C. Her presumed diagnosis was GBS, and she underwent plasmapheresis. An LP was done (table 1), and she was started on iv ceftriaxone and acyclovir. An EMG/NCV showed diffuse motor axonal polyneuropathy without sensory involvement. On day 10, she died. Autopsy revealed encephalitis with microglial nodules in the gray and white matter (figure 1A, 1B). Mononuclear perivascular inflammation was also evident. The medulla and the thalamus were most severely involved. The remainder of the autopsy showed no histologic evidence of pancreatitis, myocarditis, or hepatitis.

**Patient 5.** On 27 August, a 57-year-old man with a history of alcohol abuse was admitted with complaints of fever, vomiting, and confusion for 3 days. In the hospital, his temperature was 39°C, and examination revealed a combative man who was confused. A CT scan of the head and LP were performed (table 1). He was given iv ampicillin, ceftriaxone, and acyclovir. He improved and was discharged after 2 weeks without any sequelae.

**Patient 6.** On 23 August, a 79-year-old man presented with complaints of generalized weakness, anorexia, and confusion for 3 days. On admission, his temperature was 39.2°C, and the examination was normal except for mild muscle weakness and confusion. An LP and CT scan of the head were performed (table 1). He was started on iv ampicillin and ceftriaxone until the CSF culture was negative. He improved and was discharged to home within 11 days.

**Patient 7.** On 31 August, a 29-year-old woman presented with fever, headache, rash, nausea, vomiting, diarrhea, and weakness that started 8 days earlier. In the hospital, her temperature was 39°C, and the rest of her exam was normal except for a stiff neck and a few macular lesions on her back. The rash started on her limbs 6 days before and then spread to her trunk and back. An LP was done (table 1). She was given iv
ceftiaxone until CSF culture was negative. She was discharged to home after 5 days with mild weakness and memory loss that resolved after 3 months.

Patient 8. On 2 September, a 49-year-old man presented with a 4-day history of fever, headache, anorexia, arthralgias, weakness, and a questionable rash on his legs and arms. On admission, his temperature was 39.7°C, and his physical exam was normal. An LP was done (table 1). He was started on iv ceftriaxone. He was discharged after a week and resumed work but still felt weak for >2 weeks.

Results

We had 6 patients with encephalitis (patients 1–5 were in the ICU, and patient 6 was on a medical floor) and 2 patients with meningitis. The encephalitis group, on average, was older with a more severe presentation. Of the 6 patients, 5 had temperatures >39°C, 5 had gastrointestinal symptoms, 5 complained of weakness, and all were confused. On examination, severe muscle weakness developed clinically, and the EMG/NCV was abnormal for 4 of the 6 patients. This finding of paresis/paralysis has been reported in only 3 previous reports [4–6]. LP revealed pleocytosis in 5 of 6 patients, lymphocyte predominance in 4 of 5, polymorphonuclear cell predominance in 1 of 5, and elevated protein in 6 of 6. Patient 3 underwent spinal tap on the same day as the onset of illness, which possibly explains the early polymorphonuclear cell predominance in his first CSF sample. He had another LP 5 days later that yielded CSF with a WBC count of 8 cells/mm³ and a predominance of lymphocytes.

Four patients required ventilatory support, and 3 died. The 3 autopsies revealed encephalitis, and WNV was identified in the brain tissue by PCR and immunohistochemical (IHC) stain. Histologic features included microglial nodules, perivascular mononuclear inflammation, and focal mononuclear inflammation along cranial nerve roots exiting the medulla. One of the 3 autopsies revealed pancreatitis, although it is reported infrequently [7].

The 2 patients with meningitis had high fevers (>39°C), prodromes of nausea, vomiting, headache, weakness, and skin

Figure 1.  A. Hematoxylin and eosin–stained section of the medulla from patient 4. In the white matter adjacent to the olivary nucleus, note the microglial nodule (arrowhead) composed of histiocytes and occasional lymphocytes (original magnification, ×100). B. Microglial nodule (original magnification, ×200).
complaints. They were mentally intact and had good muscle strength. They were younger than the earlier cluster. LP revealed that both had pleocytosis with a lymphocyte cell predominance and elevated protein. Both patients recovered fully.

All 8 patients had positive serum IgM capture for WNV by ELISA; this finding was confirmed by plaque-reduction neutralization (PRNT) antibody test to exclude other cross-reacting flaviviruses (table 2). The predominant symptoms were fever, weakness, and gastrointestinal complaints (table 3). Conjunctivitis, lymphadenopathy, and sore throat were absent in our patients. Lymphopenia was present in all case patients. Liver function tests were not significantly elevated except in patient 2, who had ischemic hepatopathy. Electrocardiograms were normal for all patients except patient 2, who had a myocardial infarction.

Discussion

WNV is a member of the family Flaviviridae, single-stranded RNA viruses that are subdivided into 2 genera: flavivirus and pestivirus. There are 68 agents of flavivirus, and most are transmitted by mosquitoes or ticks (arthropods). The flavivirus genera contain 8 antigenic complexes, but only 6 have human pathogens. WNV belongs to the Japanese encephalitis complex, which includes the viruses that cause Japanese, St. Louis, and also other pathogens [8].

The major vector in NYC was the Culex pipiens mosquito, but WNV has also been previously isolated in the Aedes vexans and Anopheles mosquitoes. The source of this outbreak could have been an infected bird (either migrated or imported), infected mosquitoes, or, less probably, a viremic person. West Nile fever normally does not cause birds to become ill, but during the NYC outbreak thousands of crows died and smaller numbers of birds of other species in the greater New York metropolitan area [9]. In the past, WNV has been isolated in horses with encephalitis in Egypt, France, Portugal, Morocco, and Italy, but this is not common [10, 11]. In the past, WNV has been found in wild ixodid and argasid ticks, but their role in infecting humans is not well established [11]. It has been shown that domestic mammals either develop low-level or undetectable viremia after experimental infection. WNV has also been found in wild ixodid and argasid ticks, but their role in infecting humans is not well established [11].

The incubation period of West Nile fever is 5–15 days [9]. Symptoms typically include fever, headache, backache, and myalgia lasting 3–6 days. Other complaints reported include pharyngitis, conjunctival injection, nausea, vomiting, diarrhea, and abdominal pain. About 50% develop a nonpruritic, roseolar, or maculopapular rash on the chest, back, and arms, which lasts 1 week. Diffuse lymphadenopathy is also common [8].

Neurological infection is rarely seen but can present as aseptic meningitis, meningoencephalitis, myelitis, optic neuritis, or polyradiculitis. Severe neurologic illness is most common in the elderly and occasionally occurs in children. Extraneurologic infections can include myocarditis, pancreatitis, and hepatitis. Laboratory findings include leukopenia and, in patients with central nervous system signs, CSF pleocytosis and elevated protein [8]. The virus can be recovered from the blood of an immunocompetent febrile patient for ≈10 days. In immunocompromised patients it has been found 22–28 days after infection [12]. Peak viremia occurs between days 4 and 8 [12], but the titer is usually low (<10^{3}/mL) [11]. Standard precautions should be followed when handling specimens. One study reports that WNV could not be isolated in feces, urine, or throat washings [13].

WNV neurological infection is diagnosed by serology, PCR, or viral isolation; one of the preferred methods is IgM detection in serum by antibody-capture ELISA. The presence of IgM in CSF indicates intrathecal production. Cross-reactions with other flaviviruses occur; therefore, the presence of other en-
demic viruses must be excluded by the PRNT for antibody to WNV [11]. Serial rising antibody titers can by demonstrated by ELISA, complement fixation, neutralization, or hemagglutination inhibition tests [11]. In patients with meningoencephalitis, virus can be isolated from blood, CSF, and brain tissue (at autopsy). At the time of the outbreak, only a few laboratories could detect gene sequences by PCR or viral antigens by IHC stain [9]. Whereas the PCR technique is specific for WNV, the IHC stain will detect flaviviral antigens in the Japanese encephalitis complex. IHC staining can be performed on biopsy, necropsy, and formalin-fixed autopsy material. The virus can be grown in the laboratory by intracranial inoculation into suckling mice or on continuous cell lines of mosquito or mammalian origin [11]. WNV is classified as a biosafety level 3 agent [14]. A single laboratory-acquired infection has been reported; exposure was by the aerosolized route [15].

A case of WNV infection is confirmed by any of the following findings: (1) a 4-fold rise in the serum antibody titer; (2) isolation of virus from tissue, blood, CSF, or other body fluid or demonstration of viral antigen or genomic sequences in those sites; or (3) capture of specific IgM antibody in CSF or serum by use of ELISA. The finding of serum IgM antibodies alone should be confirmed by demonstration of IgG antibodies by use of another serologic assay, such as neutralization or hemagglutination inhibition [16].

In an outbreak in Israel during 1957, 16 of 49 patients >65 years old developed meningoencephalitis, and 4 died. Autopsy of 3 brains showed ganglion cells in various stages of necrosis, perivascular cuffing, hemorrhages, and edema [17]. The virus also was found in the brains of children during an outbreak in India [18]. A study was done in which WNV was inoculated into volunteers with neoplastic disease refractory to surgery, chemotherapy, or radiation to achieve pyrexia. The procedure was based on observations that certain viruses had an anti-neoplastic effect on experimental animals. Eighty-nine percent of the patients had no clinical illness other than fever. Eleven percent had signs of diffuse encephalitis with twitching and mental confusion, and 1 of the patients had flaccid paralysis of extremities. The neurological signs were transient, and recovery was complete [13].

During the Romanian epidemic of 1996, WNV caused mainly neurologic infections as well. There were 393 patients who had confirmed or probable WNV infection, of whom 352 had acute central nervous system infections: meningitis (40%), meningoencephalitis (44%), and encephalitis (16%). Clinically the illness was abrupt; patients had fever (91%), sudden headache (77%), neck stiffness (57%), vomiting (53%), chills (45%), and confusion (34%). In the patients with encephalitis, disorientation, and generalized weakness were important findings. Some had decreased motor power with hypotonia and a variety of deep tendon reflexes (either hypo- or hyperreflexia). Coma developed in 17%. Seventeen patients died, all >50 years old. WNV was isolated from the C. pipiens mosquito, and antibodies were found in 41% of domestic fowl in the region of the epidemic. Serosurveys of the population extrapolated that ~43,000-90,000 people were infected during the epidemic in Bucharest and 31,000 in other districts. The ratio of clinical to subclinical infection was estimated to be between 1 : 140 and 1 : 320 [19].

On 23 August 1999, the NYC Department of Health (DOH) was notified about the patients who were suspected of having encephalitis. The DOH assisted us in sending CSF and blood specimens for both PCR and serological testing. They came to our hospital and reviewed all the cases. They also surveyed the patient’s communities and their homes. It was noted that the patients were active outdoors and lived within a 2-mile radius of one another. On 3 September, IgM-capture ELISA for antibodies to the common North American arboviruses identified the agent as St. Louis encephalitis (SLE). SLE had been reported in New York State but never in NYC [20]. SLE is the leading cause of epidemic viral encephalitis in the United States. As with WNV infection, <1% of SLE infections are clinically apparent. Infection can range from a mild flu-like illness to fatal encephalitis. Advanced age is a risk factor for neurological invasion; among the elderly the proportion of encephalitis cases is higher. Examination reveals general weakness, hyperreflexia, and tremulousness, but focal weakness and convulsions are rare [21]. There is little to differentiate SLE from other viral infections of the central nervous system. Once SLE was identified, vector control with aerial and ground spraying was immediately initiated.

After reviewing specimens from the birds that had died and from our patients’ brains, the virus was determined to be WNV. The viral DNA was >99.8% identical to a WNV strain found in the brain of a dead goose in Israel in 1998. During 1998, the Israeli strain was associated with an increased pathogenicity for birds; there were no reported cases in humans, possibly because of background immunity [22]. The NYC DOH alerted all nearby hospitals to report anyone with (1) the clinical syndrome of fever, altered mental status, CSF pleocytosis, and muscle weakness; (2) presumed viral encephalitis; (3) fever and presumed GBS; and (4) aseptic meningitis [9]. After the alert, neighboring hospitals began to report suspected cases.

GBS-like presentation was unusual for WNV. GBS presents with ascending weakness generally symmetric over days to weeks. It can progress to motor paralysis and death from respiratory failure. It is usually preceded by a respiratory or gastrointestinal infection. Campylobacter jejuni is now the most frequent prior infecting organism. Other associated illnesses include infections with viruses such as cytomegalovirus, Epstein-Barr virus, HIV, and bacterial infections such as Lyme disease and Mycoplasma pneumoniae infection [23]. Both Japanese encephalitis virus [24] and dengue virus [25] are flaviviruses like WNV and have been associated with GBS. In GBS, CSF is usually acellular and has an elevated protein; 10% of patients can yield samples with 10–50 cells/mm³. EMG/NCV
shows decreased amplitudes in the motor action potential, slowed conduction velocity, or conduction block [23].

Consistent with GBS, 4 of our patients in the ICU had EMG/NCVs that showed decreased motor amplitudes, which were interpreted as motor axonopathy. The treatment is plasmapheresis or administration of iv immunoglobulin. Two of our patients received plasmapheresis: patient 4 died before any clinical effect could be appreciated, but patient 1 completed a full course of plasmapheresis and gradually recovered motor function over the next few months. It is unclear whether plasmapheresis had any beneficial impact on the natural course of the disease.

As of 21 January 2000, there were 61 cases of laboratory-confirmed WNV in the New York outbreak (45 cases in NYC, 15 in neighboring suburbs, and 1 in a Canadian tourist who visited NYC), 7 of which have been fatal [14]. The Centers for Disease Control and Prevention and the NYC DOH are now performing seroprevalence studies in the first communities to estimate the extent of this outbreak. Veterinarians are also testing for viral infection in various species to determine if they could serve as possible hosts for illness in the future. This outbreak emphasizes the important relationship veterinarians, physicians, and the public health structure should have in surveillance of disease. It stresses how small the world is and how physicians must consider pathogens not common in their regions. The entire scope of the 1999 West Nile encephalitis outbreak in NYC is yet to be determined, and we must prepare for the coming spring.

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