Israel Steiner, MD
Peter G.E. Kennedy, MD,
PhD, DSc

Correspondence to
Dr. Steiner:
isteiner@ekmd.huji.ac.il

WEST NILE VIRUS INTRODUCTION INTO THE NEW WORLD

West Nile virus (WNV) is an arthropod-borne neurotropic single-stranded RNA flavivirus capable of causing systemic and neurologic disease. The virus belongs to a family that includes important human pathogens such as dengue, Japanese encephalitis, and yellow fever viruses. Over the last 2 decades WNV has emerged as a significant burden on public health services in Europe and the Americas. Its invasion into North America in 1999 and the subsequent spread throughout the continent has stimulated intense interest in its population genetics and evolution.¹ Moreover, this event and its consequences can be viewed as a metaphor and paradigm that stresses the potential danger of modern transportation as a means of spreading pathogens into novel ecosystems.

Originally isolated in 1937 from the blood of a patient with fever in the West Nile district of Uganda, the first outbreaks of WNV disease were associated with relatively few cases, mild disease, and rural settings. However, a subsequent outbreak in Romania that occurred in 1996 and 1997 involved more than 500 reported cases, with a case-fatality rate of approximately 10%.² Additional epidemics have been reported in Russia, Israel, Greece, France, Hungary, and Italy.

Enter 1999. Up to then, WNV had never been detected in North America, but in the summer of that year the occurrence of an unusual number of deaths of exotic birds in the New York City metropolitan area was followed by an outbreak of 62 cases of encephalitis in humans, resulting in 7 deaths. Molecular analysis of viral isolates demonstrated a WNV strain closely associated with a virus isolated from a goose in Israel with 99.7% nucleotide sequence homology.³ Within several years the virus had spread throughout the mainland United States, Canada, and Mexico, and as far south as Argentina.

Between 1999 and 2010, approximately 1.8 million people were infected, with about 360,000 illnesses, 12,852 reported cases of encephalitis/meningitis, and 1,308 deaths.

The Centers for Disease Control and Prevention reported that as of December 2012, a total of 5,387 cases of WNV disease, including 243 fatalities, had been reported in that year. Of these, 51% were classified as neuroinvasive disease.⁴ These represented the largest epidemics of arboviral meningoencephalitis in US history. The impact of the virus on wildlife has also been severe, with millions of birds killed from WNV infection.

These events can be attributed to 3 factors:

1. The massive increase in intercontinental and continental travel and trade. It was suggested that an infected bird or a mosquito that arrived on a flight from Israel to New York City in the summer of 1999 imported the virus to North America. The possibility that the transmission was via a human carrier seems much less likely.
2. The ability of the virus to replicate in cells of hosts that are taxonomically divergent. WNV is maintained in nature in a cycle involving birds and mosquitoes. The birds and mosquitoes important for its perpetuation in any given area are diverse and infection has been documented in nearly 60 mosquito and 300 bird species.¹ In contrast, the related dengue virus is mainly driven by single mosquito and host species.
3. Highly focused feeding patterns of the mosquito vectors of WNV that result in unexpected host species that are important hosts for transmission.

Peak WNV transmission via mosquito bites is the most prevalent mode of transmission and occurs in the summer and fall, between July and October, but cases have also been reported in April and December. Cases of infection have been documented following person-to-person transmission, breast-feeding, blood transfusion, and respiratory aerosol.

Both age (above 50 years) and immunosuppression (mainly in organ transplanted patients) are risk factors for developing WNV meningoencephalitis. Other factors include homelessness, a history of cardiovascular or chronic renal disease, and hepatitis C virus infection. Host genetic factors also contribute to the risk of

From the Department of Neurology (I.S.), Rabin Medical Center, Petah Tikva, Israel; Department of Neurology (I.S.), College of Medical, Veterinary and Life Sciences, Glasgow University; and Institute of Neurological Sciences (P.G.E.K.), Southern General Hospital, Glasgow, Scotland, UK.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

developing severe neuroinvasive disease. The disease in immune-suppressed patients is more severe.

Infections in humans are predominantly subclinical, but can result in meningoencephalitis and death. However, only about 1 in 150 infected individuals develop neuroinvasive disease as well as meningitis and encephalitis. WNV may also cause an acute flaccid paralysis in a severe poliomyelitis-like syndrome that has a poor long-term outcome. Among older patients who survive, as many as 50% may have significant postviral morbidity for at least a year and an increased risk of death for up to 3 years following infection.

The gold standard for diagnosis remains serology of serum and CSF.⁵ WNV immunoglobulin M antibody can be detected in 95% of infected patients within a week. Its presence in the CSF is due to intrathecal synthesis and is associated with neuroinvasive disease. Reverse transcriptase PCR of serum or CSF is not generally useful since peak viremia occurs 3–4 days before symptom onset, resulting in poor sensitivity. The CSF is pleocytotic and polymorphonuclear or lymphocytic cells can predominate with elevated protein and normal glucose levels, with the characteristics of an “aseptic meningitis.” The MRI findings in patients with WNV neuroinvasive disease are extremely variable, ranging from unremarkable to pathology involving gray or white matter.

Several rapid tests have been developed for blood donor screening using nucleic acid testing.

It was suggested that IV immunoglobulin (IVIg) treatment might be beneficial in WNV infection, and there was a study that examined the effect of an Israeli-produced IVIg preparation, based on the hypothesis that it might be abundant in anti-WNV antibodies. However, this was not the case and currently there is no specific therapy, nor are there any ongoing clinical trials that test other therapeutic modalities.⁴

Thus, the introduction of a relatively old and known pathogen into a new ecosystem resulted in an epidemic that is ongoing. Although this has stimulated intensive research into the biology of the pathogen, its vectors, transmission mode, and human disease, there are no specific therapeutic measures to control the infection and prevent its consequences. The hope that the epidemic is declining, based on the reduction in the number of annual cases between

2004 and 2010, led, in part, to a cutback in the drive to develop prophylactic and therapeutic measures against the disease, but this hope was dispelled by the record large epidemics of 2011 and 2012.

The constant introduction of pathogens to new ecosystems in our globally connected planet is inevitable. Many viruses of public health concern such as Japanese encephalitis, Rift Valley fever, tick-borne encephalitis, and chikungunya can be transported to the new world, and there are new world pathogens, including Venezuelan equine encephalitis, that can go east. Gaining an understanding of the ecology of zoonotic viruses, combined with fast-developing recombinant vaccine technologies, should provide the basis of more effective strategies to prevent the emergence of newly introduced pathogens.

AUTHOR CONTRIBUTIONS

Israel Steiner: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Peter Kennedy: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

I. Steiner serves on the editorial boards of the *Journal of Neurovirology* and the *Journal of Neurological Sciences*; serves on a data safety monitoring board for Actelion Pharmaceuticals Ltd. and Hoffman LaRoche; and has received research support from the Israel Science Foundation, the Israeli Ministry of Health Chief Scientist, and Teva. P. Kennedy has served on a scientific advisory board for Sanofi Pasteur MSD; serves on the editorial boards of the *Journal of Neurovirology*, the *Journal of Neuroimmunology*, *Neurocritical Care*, the *Scottish Medical Journal*, the *Journal of Neuroimmune Pharmacology*, and the *Journal of Neuroparasitology*; and receives royalties from the publication of *The Fatal Sleep* (Luath Press Ltd., 2007). Go to Neurology.org for full disclosures.

REFERENCES

1. Pesko KN, Ebel GD. West Nile virus population genetics and evolution. *Infect Genet Evol* 2012;12:181–190.
2. Tsai T, Popovici F, Cernescu C, Campbell G, Nedelcu N. West Nile encephalitis epidemic in southeastern Romania. *Lancet* 1998;352:767–771.
3. Davis CT, et al. Phylogenetic analysis of North American West Nile virus isolates, 2001–2004: evidence for the emergence of a dominant genotype. *Virology* 2005;342: 252–265.
4. CDC. West Nile Virus. Available at: <http://www.cdc.gov/ncidod/dvbid/westnile/>. Accessed December 14, 2012.
5. Tyler KL, Pape J, Goody RJ, et al. CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. *Neurology* 2006;66:361–365.

Neurology®

West Nile virus introduction into the new world

Israel Steiner and Peter G.E. Kennedy

Neurology 2013;81;1441-1442

DOI 10.1212/WNL.0b013e3182a840ad

This information is current as of October 14, 2013

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/81/16/1441.full>

References

This article cites 4 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/81/16/1441.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Viral infections

http://n.neurology.org/cgi/collection/viral_infections

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:

<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2013 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.