

Equine West Nile Encephalitis: Epidemiological and Clinical Review for Practitioners

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1. Introduction

The first occurrence of West Nile (WN) virus in the Western Hemisphere was in 1999. In the fall of that year, WN virus was identified as a cause of encephalitis in 25 horses in two New York counties.¹ During the 2000 transmission season, 60 equids in seven northeastern states were confirmed cases of WN viral encephalitis.² In 2001, the virus was identified in most states in the eastern half of the United States, and 738 clinically apparent equine infections occurred (Fig. 1).³ Although 20 states had at least one confirmed case of equine WN encephalitis in 2001, the epizootic was dominated by Florida and Georgia; cases in those states accounted for more than 75% of the total. During the 2001 outbreak, 48 horses were admitted to the Alec P. and Louis H. Courtelis Equine Teaching Hospital, University of Florida, as suspect for WN virus infection. This report summarizes our current knowledge about the biology of WN virus, its clinical presentation, diagnosis, and prevention strategies for horses.

2. Virology and Epizootiology

WN virus is a member of the *Flaviviridae* family and belongs to the Japanese encephalitis (JE) serogroup of the genus *Flavivirus*, along with St. Louis encephalitis virus, JE virus, and others.⁴ St. Louis encephalitis virus is widespread in the Americas and has been responsible for epidemics of febrile illness, meningitis, and encephalitis in humans, but it has not been reported as a significant pathogen of horses.⁴ WN viral infection causes encephalitis in horses and humans. This virus is widespread, but until 1999 it was exotic to the United States.⁵ The incursion of WN virus in the United States represents the first clinically significant flavivirus pathogen encountered by the resident equine population.

Although originally isolated from human blood in Uganda, Africa, in 1937, WN virus is maintained in nature primarily by transmission between birds and mosquitoes.⁴ WN virus is endemic year-round in parts of Africa, the Middle East, and Asia, with occasional seasonal spread, coincident with migrating birds and mosquito activity, into more temperate regions such as France, Italy, and eastern Europe.⁴

NOTES

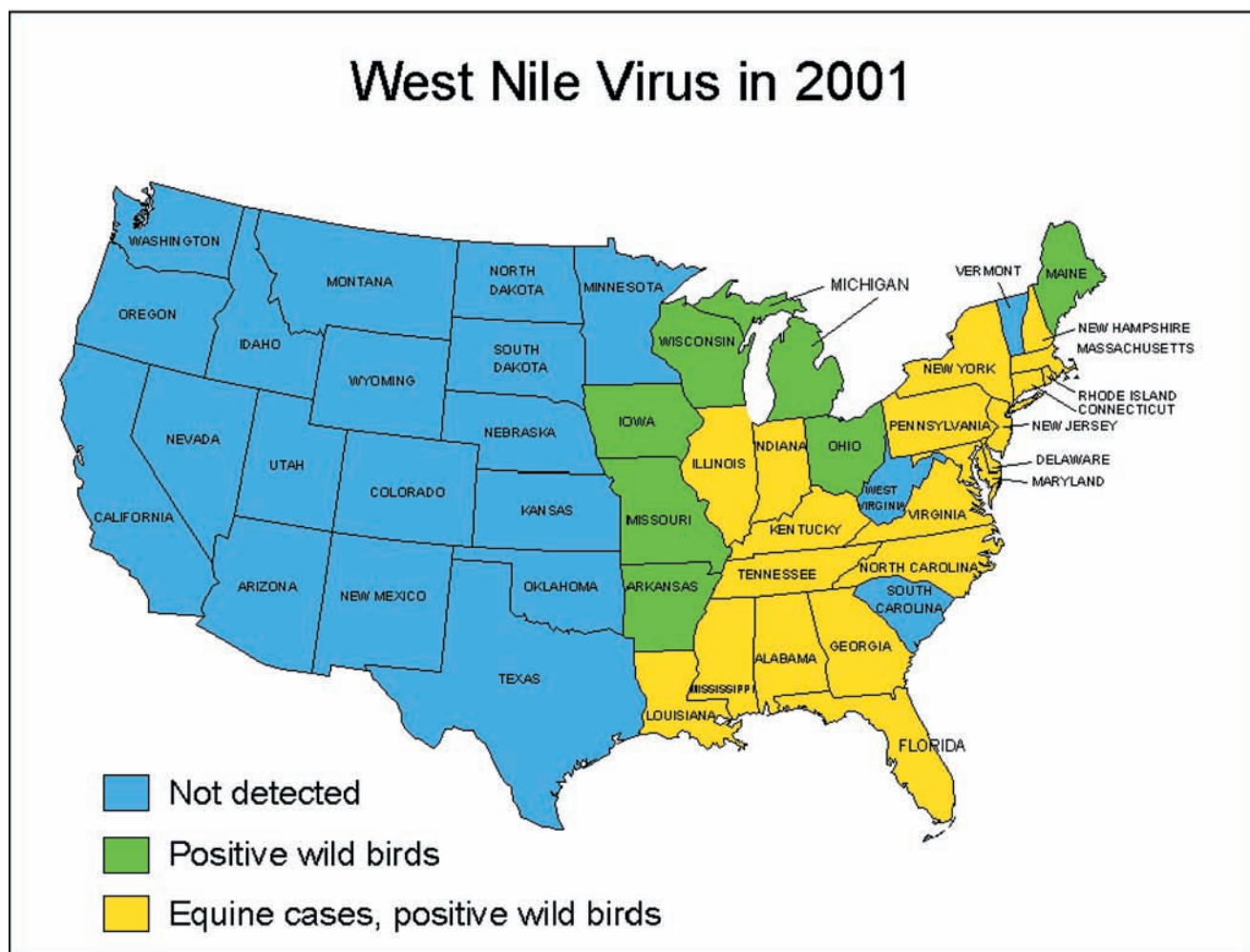


Fig. 1. Map of West Nile Virus throughout the United States in 2001.

In the United States, WN transmission in the north-eastern states follows a seasonal pattern, peaking in early autumn. The fact that WN virus has now appeared in the southeastern states poses a risk for year-round viral transmission. In fact, the onset date of the 2001 outbreak in Florida began in June and extended through December. Reporting during the months of January and February 2002 has revealed year-round activity in the Southeast.

WN virus amplifies to high titers in competent avian and mosquito species.^{4,6-8} Mosquito vectors that can "bridge" between avian and mammalian species initiate spread of infection beyond the reservoir avian hosts. Horses and humans, while susceptible to clinically apparent WN infections, are likely incidental, dead-end hosts because of low levels of viral amplification in these species. Limited evidence acquired to date does not support a role for any mammalian species in WN virus amplification or spread to new areas.^{9,10}

Until recently, disease in birds naturally infected with WN virus was not observed. Reports of deaths

in geese in Israel during 1997–2000 and recent U.S. experiences indicate a change in viral biology.¹¹ In 1999, the incursion of WN virus into the Western Hemisphere was first recognized because of fatal infections in zoo birds and massive numbers of crow deaths near New York City.¹² Genetic studies revealed that the New York 1999 strain was closely related to the strain isolated in Israel in the prior year.¹³ During the past three transmission seasons in the United States, dead crow sightings and virus identification in crows and other corvids have correlated strongly with new foci of WN virus activity.¹⁴ Recent studies indicate that numerous native North American bird species can amplify WN virus to titers easily capable of mosquito transmission.¹⁵ Experimental crow-crow transmission of WN virus in the absence of mosquito vectors has been reported.¹⁶ Virus-permissive native bird species are crucial for WN virus maintenance in nature and for carrying the virus to new areas through migration flyways. Although WN virus has been identified in dozens of native U.S. bird species,¹⁷ the

birds most pivotal to spread and maintenance of WN virus in the Americas have not been identified.

Mosquitoes commonly transmit WN virus among birds and are thought to be the primary insect vector for infection, although both hard and soft ticks have been shown to effect transmission in certain ecosystems. In the United States, WN virus has been identified in numerous mosquito species, including members of the genera *Culex*, *Aedes*, *Anopheles*, *Ochlerotatus*, and *Psorophora*.⁶ Whereas some mosquito species (e.g., *Culex pipiens*, *C. restuans*) feed exclusively on avian hosts, others such as *C. salinarius*, *Aedes vexans*, and *Ochlerotatus japonicus* are candidate bridge vectors for transmission between birds and mammals.⁶ Despite the range of ecologic and climatic conditions in the United States, the variety of WN virus-permissive native avian and mosquito hosts forecast few limitations for geographic spread.

Historically, WN virus infections in humans often presented as mild, acute febrile disease, sometimes accompanied by lymphadenopathy and rash. Serologic surveys revealed that many human infections were asymptomatic. Large-scale epidemics of disease in humans have occurred sporadically in endemic locations such as Israel and South Africa, but before the mid- 1990s, aseptic meningitis and encephalitis were not common signs of WN virus infection. In contrast, manifestations of encephalitis, particularly in the elderly, have been prominent in recent focal outbreaks of human WN disease in Romania (1996), Russia (1999), and the northeastern United States (1999–2001).¹⁸ Approximately 150 human cases of WN virus encephalitis have been identified in the United States during 1999–2001.

Few outbreaks of WN disease in horses were documented before the 1990s. In 1959, WN virus was isolated from the brain of an encephalitic horse in Egypt.¹⁹ WN virus was determined to cause encephalitis in horses in the Camargue region of France in 1962–1965, but further occurrence in that area was not reported for almost 40 yr.²⁰ Reports of WN viral disease in horses in the past decade include 92 cases in Morocco in 1994,²¹ 18 in Israel in 1998,²² 14 in Italy in 1998,²³ and 76 in France in 2000,²⁰ as well as the U.S. cases reported in 1999, 2000, and 2001.^{1–3,24} The number of affected equids in the United States in 2001 exceeds the total of all prior reported clinical cases of WN encephalitis in horses worldwide. In addition, the recurrence of cases in the same geographic location in sequential years has been a unique feature of the U.S. experience with this virus. Evidence from serosurveys confirms that asymptomatic WN infections occur in horses.²⁵ Factors that influence progression of disease in exposed individuals are not known, but elderly horses are more likely to manifest severe illness and have a fatal outcome.

Taken together, the behavior of WN viral infections in birds, humans, and horses during the most recent decade does not mirror prior experiences.

Entrance into new ecologic niches, encounters with naive populations, changes in climatic pressures, and/or alterations in the virus genome are likely factors contributing to recent disease outbreaks in humans, horses, and birds.

3. Clinical Presentation

In horses, WN virus causes a polioencephalomyelitis (infection of grey matter), with lesions increasing in number in the mid-brain, progressing through the hind brain, and frequently increasing in severity distally throughout the spinal cord.^{26–28} This is an important feature that distinguishes WN virus disease clinically from Eastern equine encephalitis (EEE), Western equine encephalitis (WEE), and Venezuelan equine encephalitis. With EEE and WEE, the severity is ascending in nature with a predilection for the cerebral cortex, with signs largely characterized by abnormalities of mentation, behavior, and seizure. With WN virus disease, spinal signs are common, and consideration of other differential diagnoses with this clinical presentation is important.

In prior reported WN outbreaks, horses primarily presented with sudden or progressive ataxia.^{1,2,20–24} Fever, periods of hyperexcitability, apprehension, somnolence, listlessness, and depression were the primary signs reported. Fever was reported in the French outbreak²⁰ but not in the Italian outbreak.²³ These two outbreaks were characterized mainly by spinal cord signs of ataxia and muscle rigidity, usually more severe in the hind limbs. Complete, flaccid paralysis, when present, could involve one or all four limbs. Infrequently, head tilt was observed. Mortality in the 2000 equine outbreak was 38%, with few residual problems reported in surviving horses.²

During the summer and fall 2001, 48 horses presented at the Alec P. and Louis H. Courtelis Equine Teaching Hospital at the University of Florida for signs consistent with WN virus. Similar to the clinical signs of the previous outbreaks, fasciculations of facial and neck muscles, along with varying degrees of pelvic limb ataxia and weakness, were common clinical signs. Signs usually were bilateral but could present with marked asymmetry. Not previously reported was also blindness and weakness of the tongue. In many of the cases, there seemed to be a recrudescence of mild-to-moderate clinical signs 2–3 days after acute signs abated. Of these horses, over half received the first WN virus vaccine injection, and 1 received both initial injections 6 wk previous to onset of clinical signs.^a The overall mortality rate in these horses was 24%. The mortality rate in horses that were recumbent was greater than 60%.

4. Differential Diagnoses

Because there are no pathognomic signs that distinguish WN virus infection in horses from other CNS diseases, a full diagnostic work-up is imperative.

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Infectious CNS diseases that should be considered include alphaviruses, rabies, equine protozoal myeloencephalitis (EPM), and equine herpes virus-1. Less likely candidates are botulism and verminous meningoencephalomyelitis (*Halicephalobus gingivalis*, *Setaria*, *Strongylus vulgaris*).^{29–31} Non-infectious causes to consider include hypocalcemia, tremorigenic toxicities, hepatoencephalopathy, and leukoencephalomalacia. In alphaviral encephalitis and rabies, signs of cerebral involvement are characterized by behavioral alterations, depression, seizure, and coma. The appearance of seizure and coma is rare in horses infected with WN virus. Frequently, motor function is abnormal in EEE and WEE. In WN virus disease suspects, circling and propulsive walking may occur, but head pressing is rare. Cranial nerve signs in EEE and WEE are also common, including head tilt, pharyngeal/laryngeal dysfunction, and paresis of the tongue. Other clinical signs of alphavirus encephalitis common with WN virus infection are muscle fasciculations, hyperaesthesia, excitability, blindness, somnolence, weakness of the tongue, and progression to recumbency. Mortality in non-vaccinated horses with EEE is high, approximately 80–100% (as is rabies). The incidence of WEE in horses is fairly low in the United States, but mortality and severity of clinical signs would be more similar to WN virus. Differentiation from rabies is quite problematic because clinical signs in horses with rabies frequently include ataxia, weakness, or gait abnormalities. Alphaviruses, rabies, *H. gingivalis* infection, hepatoencephalopathy, and leukoencephalomalacia are rapidly progressive with cortical signs. Although there are periods of somnolence, blindness, and some cranial nerve deficits, WN virus horses seem to become rapidly recumbent or stabilize over several days. Spinal disease caused by EPM is a more difficult differential if horses with WN virus are not febrile and do not exhibit excessive muscle fasciculations.

5. Laboratory Testing

Confirmation of WN virus infection with encephalitis in all 48 cases presented to the Alec P. and Louis H. Courtelis Equine Teaching Hospital at the University of Florida was based on criteria established by the National Veterinary Services Laboratories in Ames, Iowa, in conjunction with Centers for Disease Control in Atlanta, Georgia.² This includes probable case definition based on clinical signs (as described previously) in horses from a county in which WN virus has been confirmed in the current calendar year in mosquitoes, birds, humans, or horses. Two tests are used to confirm exposure to WN virus. The IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) and plaque neutralization test measure IgM and IgG, respectively. Other means of confirmation included postmortem detection of WN virus by polymerase chain reaction, culture, and immunohistochemistry in tissues of the CNS. The

method of choice for WN virus nucleic acid in equine tissue is the reverse transcription-nested polymerase chain reaction because of exquisite sensitivity of this method and the relatively low viral load in equine tissues.³²

Ancillary diagnostic testing should include complete blood count, serum biochemistry analysis, and cerebrospinal fluid (CSF) analysis.^{29–31,33} For the most part, complete blood count and serum biochemistry profiles of WN virus horses are normal. Horses may present with a mild absolute lymphopenia. Horses can have elevated muscle enzymes secondary to trauma and prolonged periods of recumbency. CSF cell counts protein can be elevated. Differentials on CSF of WN virus horses are consistently mononuclear, whereas EEE infections are primarily neutrophilic during the initial stages of disease.

Serum titers should be evaluated for recent exposure to other encephalitides, including EEE, WEE, equine herpes virus-1, and paired titers are necessary in vaccinated horses. Because WN virus can present with asymmetrical weakness and ataxia, Western blot testing for EPM should also be performed on serum and CSF. The integrity of the blood-brain barrier (BBB) is unknown at this time, making interpretation suspect. Horses with positive CSF fluid could theoretically be positive as a result of leakage of serum components through damaged blood-brain barrier rather than intrathecal production.

6. Treatment, Case Management, and Outcomes

Treatment of WN virus encephalomyelitis is supportive. The survival rate of this infection was high for acute encephalitis, and in many cases, horses appear to begin recovery between 3 and 5 days after onset of signs. This fact makes it difficult to accurately assess the affect of any pharmacological intervention in the face of resolving clinical signs. Flunixin meglumine^p (1.1 mg/kg, q 12 h, IV) early in the course of the disease seems to decrease the severity of muscle tremors and fasciculations within a few hours of administration. To date, much of the mortality in WN virus horses at the Veterinary Medicine Teaching Hospital resulted from euthanasia of recumbent horses for humane reasons. Recumbent horses were mentally alert and would frequently thrash, sustaining many self-inflicted wounds and posing risk to personnel. Therapy of recumbent horses is generally more aggressive and may include dexamethasone sodium^c (0.05–0.1, q 24 h, IV) and mannitol^d (0.25–2.0 gm/kg, q 24 h, IV). Detomidine hydrochloride^e (0.02–0.04 mg/kg, IV or IM) is effective for prolonged tranquilization. Low doses of acepromazine^f (0.02 mg/kg, IV or 0.05 mg/kg, IM) provide excellent relief from anxiety in both recumbent and standing horses. Until EPM is ruled out, prophylactic institution of anti-protozoal medications is recommended. Other supportive measures may include

oral and IV fluids and antibiotics for treatment of infections that frequently occur in recumbent horses (wounds, cellulitis, and pneumonia).

7. Prevention and Control

Practices to lower risk of occurrence of equine WN encephalitis include avoiding exposure to infected mosquitoes and stimulating a protective immune response before encountering the virus. Results of a case control study to identify specific risk factors for exposure to WN virus during the 2000 outbreak in the northeastern United States did not highlight any individual animal or management factors that posed a statistically significant risk.²⁵ Nonetheless, a tendency against exposure was present in horses housed indoors at night, and a positive tendency was present in horses used for pleasure riding compared with those used for racing or breeding. Spatial analysis of horses exposed to WN in 2000 indicated that cases were clustered, but that the risk for an individual animal within the cluster was random.²⁵ Control efforts currently suffer from lack of knowledge about the biology of WN virus in U.S. ecosystems, and in some jurisdictions, delays to initiate mosquito control (e.g., after first human clinical case) or strong objections to use of mosquito adulticides. As specific bridge vectors for equines and humans are identified, appropriate methods to reduce mosquito pressures will be possible.

An inactivated virus vaccine for use in horses was granted a conditional license in August 2001.^a The vaccination protocol specifies two doses of vaccine, administered IM, 3–6 wk apart. Vaccination was employed in the fall of 2001, concurrent with virus activity in the eastern United States. Therefore, horses were unable to receive both vaccine doses and develop a response to the vaccine before virus exposure. In over 700 cases of WN encephalitis in 2001, more than 100 horses were reported to have received at least one dose of vaccine.³ Of these, only three horses, including one case seen at the University of Florida, had a complete vaccination series within a time frame reasonable to expect protective antibodies. Determination of clinical efficacy of the vaccine awaits a new transmission season.

The presence of vaccine-induced antibodies can complicate interpretation of diagnostic serology tests. Based on limited data, the current WN vaccine product does not seem to stimulate IgM class antibodies in vaccinates at the level of the established cut-off for recent exposure.^{g,h} Confirmation of these findings are currently underway. Until further investigation, detection of WN-specific IgM antibodies in acute phase serum samples may continue to provide evidence of recent exposure to live virus and facilitate diagnosis of clinical cases.

8. Conclusion

As of the end of the 2001 vector season, it is apparent that WN virus is established in the United States. This pathogen will likely remain a disease risk for horses in a manner similar to EEE and WEE viruses. Despite a lack of evidence to support a role for horses in virus transmission, the disease has precipitated some interstate and international trade restrictions. Continuing efforts are being expended to negotiate transparent and science-based requirements for equine movement. The new season should bring new information regarding the continued spread and control of WN virus in horses. Regardless of the protection status of the new vaccine, post-vaccination WN virus suspect horses should continue to be tested for the presence of IgM and IgG levels specific for the virus. In addition, all WN virus suspect horses that are euthanized should have a post-mortem analysis to confirm WN virus infection and rule out other significant public health risks such as rabies and other viral encephalitides.

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