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REVIEW ON: STUDY OF PATHOPHYSIOLOGY AND DIAGNOSIS OF WEST NILE VIRUS

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Abstract:
West Nile virus (WNV) is an important zoonotic flavivirus responsible for mild fever to severe, lethal neuroinvasive disease in humans, horses, birds, and other wildlife species. Since its discovery, WNV has caused multiple human and animal disease outbreaks in all continents, except Antarctica. Infections are associated with economic losses, mainly due to the cost of treatment of infected patients, control programmes, and loss of animals and animal products. The pathogenesis of WNV has been extensively investigated in natural hosts as well as in several animal models, including rodents, lagomorphs, birds, and reptiles. However, most of the proposed pathogenesis hypotheses remain contentious, and much remains to be elucidated. At the same time, the unavailability of specific antiviral treatment or effective and safe vaccines contribute to the perpetuation of the disease and regular occurrence of outbreaks in both endemic and non-endemic areas. Moreover, globalisation and climate change are also important drivers of the emergence and re-emergence of the virus and disease. Here, we give an update of the pathobiology, epidemiology, diagnostics, control, and "One Health" implications of WNV infection and disease.

KEYWORDS: *West Nile virus, One Health, epidemiology, outbreak*

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INTRODUCTION:

WNV was first isolated from a febrile patient from the West Nile district of Northern Uganda in 1937(1) . The patient presented in the setting of a large epidemiologic study of yellow fever virus; however, inoculations of mice with the patient's serum resulted in the isolation of a virus with physical and pathologic properties similar to those of two flaviviruses, St. Louis encephalitis virus and Japanese B encephalitis virus, and sharing immunological relationships with these viruses. Although the index patient presented with fever only, these first studies with the newly discovered virus indicated that pathology primarily involved the central nervous system (CNS), suggesting its neurotropic nature. The epidemiology and ecology of WNV was first characterized in detail during several outbreaks in the Mediterranean basin in the early 1950s and 1960s. young children represented the majority of cases. During this outbreak the various clinical features associated with infection were first described in detail, with the main symptoms being fever, headache, myalgias, anorexia, abdominal pain, exanthems, and vomiting; lymphadenopathy, angina, and diarrhea were somewhat less common. Several large outbreaks in Egypt between 1951 and 1954 led to a further understanding of the ecology, epidemiology, and clinical characteristics of WNV (2). The vector-borne nature of the virus had been suggested several years earlier on the basis of ecology and transmission studies. In addition, the discovery in Egypt that the virus could be isolated only from mosquitoes, and not from other arthropods, suggested mosquitoes as the primary vector; this was substantiated by the demonstration that only mosquitoes could maintain a vector cycle by infection of a host through feeding, followed by subsequent transmission through biting (3) . At the time, persons with incurable neoplasms were sometimes inoculated with viruses causing pyrogenic infection in an effort to inhibit the growth or spread of the cancer (4).

Etiology:

The West Nile virus infects humans following a mosquito bite. The *Culex* species of mosquito is the most common vector. Besides humans, the West Nile virus can infect birds, horses, dogs, and many other mammals. Wild birds may be the optimal hosts for harboring and enabling amplification of the virus. Humans are considered accidental dead-end hosts due to the low and transient viral levels in the bloodstream. Additional and rare means of transmission include infected donor blood, organs, breast milk, or transplacental infection.

About 1% of individuals will develop serious symptoms and the overall morbidity is increased in people over the age of 50. The most common complications are neurological. Unfortunately, the lack of federal funding has meant that active surveillance of this virus is not maintained in many states (5).

EPIDEMIOLOGY:

The original outbreaks of the virus showed a typically self-limited and minor illness. In the mid-1990s West Nile virus became correlated with severe neurologic disease. Based on a comprehensive literature review in 2013, meningitis and encephalitis (neuroinvasive disease) were present in less than one percent of infected patients with a mortality of 10 percent. West Nile fever is present in 25% of those infected; the remaining 75% show few to no symptoms. This fact leads to the likely vast underreporting of West Nile virus infections. Outbreaks tend to be associated late summer and fall due to the mosquito vector's life cycle and the amplification from the bird-mosquito-bird cycle. In warmer climates, cases can occur throughout the year (6). In the Western Hemisphere, most human WNV disease has occurred in the United States. Since the virus was detected in New York from 1999 through 2004, 16,706 cases have been reported to the Centers for Disease Control and Prevention (CDC); 7,096 of these were classified as neuroinvasive disease, 9,268 as West Nile fever (WNF), and 342 had other or unspecified clinical presentation (reported through June 8, 2005; the proportion of total cases reported that are neuroinvasive disease is artificially higher than what is believed to occur naturally since neuroinvasive disease is more likely to be reported than WNF or asymptomatic infection) (table1). Transmission of WNV has spread dramatically from New York to the north, south, and west (fig1). From 2002 to 2003, the most intense transmission shifted from the Midwest and south-central states to the western plains and Front Range of the Rocky Mountains. In 2004, most WNV disease cases were reported in California, Arizona, and western Colorado, but foci of highest incidence were scattered across the United States (fig 1). In the East, WNV transmission recurred for 6 consecutive years with the highest number of human disease cases reported in 2003, indicating that WNV disease has become seasonally endemic. In Canada, transmission of WNV to humans has been documented in Quebec, Ontario, Manitoba, Saskatchewan, and Alberta, and WNV-infected birds have also been found in New Brunswick and Nova Scotia. Evidence of WNV transmission has been reported from the Cayman Islands, Jamaica, Dominican Republic, Mexico, Guadeloupe, El Salvador, Belize, Puerto Rico, and

Cuba, but only 1 human case has been reported from Mexico and 1 from the Cayman Islands (7).

Table 1: Human West Nile virus disease cases by clinical syndrome, United States, 1999–2004

Year	Total cases	Neuroinvasive cases	West Nile fever cases	Other clinical	Deaths
1999	62	59	`3	0	7
2000	21	19	2	0	20
2001	66	64	2	0	9
2002	4156	2946	1162	48	284
2003	9862	2866	6830	166	264
2004	2539	1142	1269	128	100
Total	16706	7096	9268	342	666

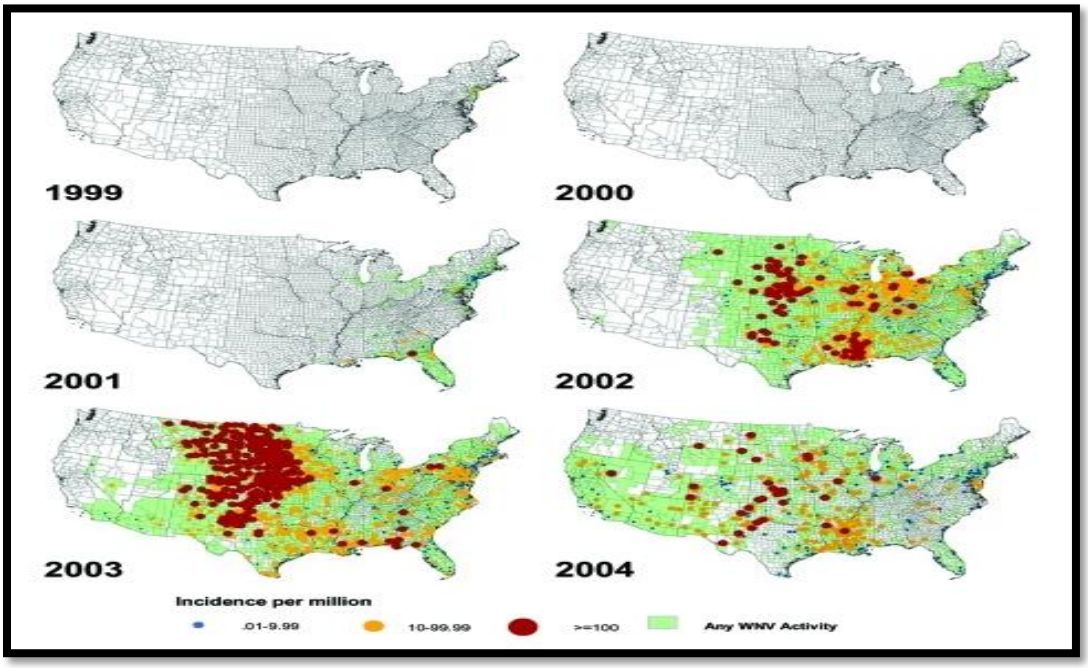
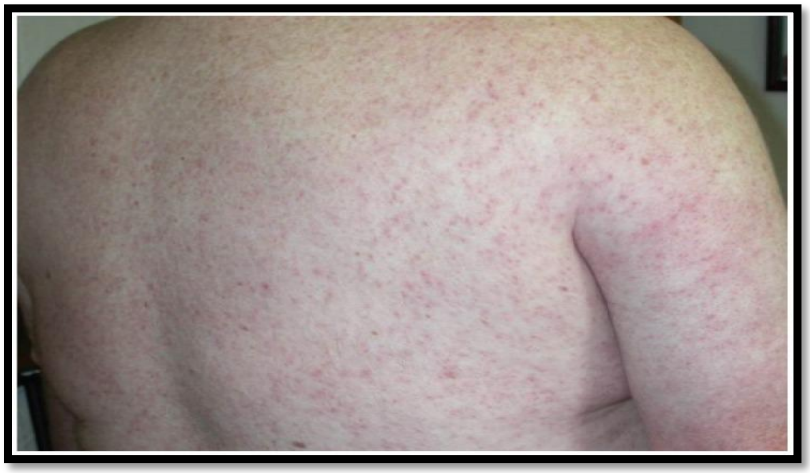


Fig1: Reported incidence of neuroinvasive West Nile virus disease by county, United States, 1999–2004.

Clinical Syndromes Associated with Infection:

WNF is the predominant clinical syndrome seen in most infected persons. All ages may be affected, but data suggest that the proportion of WNF may be higher among younger individuals (8). Following an incubation period of approximately 2–14 days, infected persons typically experience the abrupt onset of fever, headache, fatigue and myalgias. Gastrointestinal complaints, including nausea and vomiting, have been frequently described and may lead to dehydration.

WNF may sometimes be associated with a rash, which tends to be morbilliform, maculopapular and non-pruritic and predominates over the torso and extremities, sparing the palms and soles. (Fig:2). The rash may be transient, lasting less than 24 h in some persons. Interestingly, this rash appears to be more frequently seen in WNF than in more severe illness manifestations (WNM or WNE). In addition, rash is more frequently observed among younger persons than among older persons. These findings raise the question as to whether the presence of a rash correlates with host immune or cytokine response to infection (9).



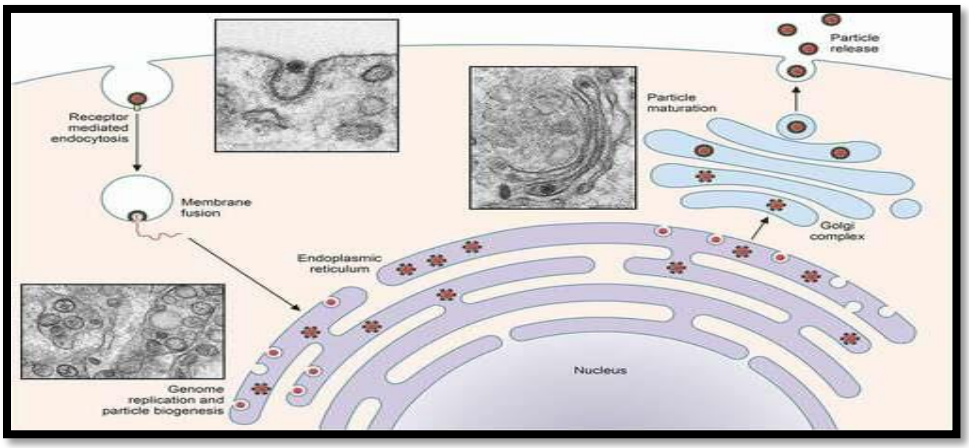
(fig 2): Diffuse maculopapular rash associated with West Nile virus infection.

Pathogenesis and Pathology:

Seroprevalence studies suggest that while the majority of WNV infections are asymptomatic, approximately 20 to 30% of infected individuals develop flu-like clinical manifestations characterized as WNV fever. In a subpopulation of individuals (approximately 1 in 150), a neuroinvasive disease develops. The clinical features of severe WNV infection vary and include severe headache, ocular manifestations, muscle weakness, cognitive impairment, tremors, and a poliomyelitis-like flaccid paralysis The mortality rate following neuroinvasive infection is approximately 10%(10) . Rodent models have provided insight into the mechanisms of WNV dissemination and pathogenesis. Following peripheral inoculation, initial WNV replication is thought to occur in skin Langerhans dendritic cells. These cells migrate to and seed draining lymph nodes, resulting in a primary viremia and subsequent infection of peripheral tissues such as the spleen and kidney (11).

Virus cell host interactions:

WNV replicates in cells of different origin (insect, mammalian, and avian), and, thus, it uses either conserved or different receptors for viral entry depending on the cell. The infection is initiated by the binding of the virion to its cellular receptor (fig 3). As detailed below, glycosaminoglycans, c-type lectins like DC-SIGNR, the mosquito mosGCTL-1, TIM phosphatidylserine binding protein, integrin $\alpha_v\beta_3$, and the ubiquitin ligase CBLL1 have been proposed as cellular receptors for WNV, and proteins from the G-coupled receptor kinase (GRK) family have been reported to act as cofactors that facilitate viral entry and replication.



(fig 3): **Schematic view of WNV infectious cycle**.

Diagnosis:

Cranial MRI appears to be superior to CT for distinguishing central nervous system inflammation. In the 1999 New York outbreak, none of the 43 CT scans showed evidence of acute disease, whereas 31% of those scanned with MRIs had abnormal findings suggesting inflammation. Spinal fluid analyses in this study showed a normal glucose level and elevated protein level with a lymphocytic pleocytosis (12). Both electromyograms and nerve conduction studies may be useful in patients that exhibit neuromuscular abnormalities. The most common diagnostic method used is IgM-capture enzyme-linked immunosorbent assay (ELISA). The sensitivity of this test is 95%–100% in both serum and spinal fluid. In most cases, the IgM is detectable in the serum and cerebrospinal fluid by onset of disease (communication from CDC). This testing methodology is available through state and local health departments. WNV-specific IgM antibody is not detected until the end of the viremic period, which may approach the fourth day of illness. High IgM WNV antibodies in a person with encephalitis or meningitis likely represent infection; however, the IgM may persist from several months to more than a year. Additionally, an intrathecal IgM specific for WNV strongly suggests central nervous system infection, as humoral IgM antibodies do not cross the blood-brain barrier. There is a close antigenic relationship among the flaviviruses. Recent immunization with yellow fever or Japanese encephalitis vaccines may result in false positive results on IgM antibody testing for WNV. Other infectious agents may also cross-react with WNV testing, including dengue, St. Louis encephalitis, and other arboviruses. However, a four-fold change in neutralizing antibody titer should still be sought to provide a specific diagnosis of WNV infection. CDC-defined IgM and IgG ELISAs that use specified antigens are preferred and are available from many state laboratories. Plaque reduction neutralization tests comparing the titers to cross-reacting agents can help determine false-positive IgM antibody capture test results. Both viral culture and polymerase chain reaction (PCR) testing, albeit promising, have been shown to be less sensitive that the ELISA for routine testing. Diagnosis can also be made by brain biopsy from surgery or autopsy. The pathological findings in fatalities have shown diffuse inflammation of the brain and spinal cord with small hemorrhages, perivascular cuffing, and extensive neuronal degeneration. These findings result from WNV replication causing injury, cytotoxic response, and inflammation NAATS have the potential to simplify and improve the diagnosis of flavivirus CNS infections. PCR that uses degenerate primers that detect regions conserved across a wide variety of flaviviruses and primers that are WNV specific should provide a sensitive and specific diagnostic method, but its value relative to IgM assays needs further evaluation. Development of “real-time” or TaqMan PCR may provide a rapid diagnostic test for evidence of WNV in CSF. Currently, neither NAATs nor virus isolation from CSF are as sensitive as ELISA for identifying an acute WNV infection. But a positive test may distinguish WNV encephalitis or meningitis from infections due to treatable pathogens. Because these methods would be done in hospital-based microbiology laboratories that routinely use NAATs for other infectious diseases, clinicians could make a specific diagnosis within hours of collecting CSF samples. In contrast, traditional serology-based diagnostic methods may take one to several weeks to perform and are only available at a few experienced laboratories. Although the WNV IgM ELISA and NAAT are not approved by the US Food and Drug Administration for patient management, they are useful in identifying the cause of epidemic encephalitis after more treatable causes of encephalitis are ruled out. WNV may be isolated from human serum, blood, and CSF early in the febrile stage and from brain obtained during biopsy or autopsy. Virus isolation is made by inoculation of multiple substrates, including neonatal mice and both mammalian and mosquito cell lines. Only laboratories with extensive experience in flavivirus isolation and a biosafety level 3 containment facility should attempt virus isolation. If virus isolation is to be attempted, or if clinicians are uncertain about the type of testing needed, specimens should be frozen at -70°C or placed on dry ice immediately. Storage and shipment at this temperature will prevent degradation of the virus and nucleic acids. To date, no WNV isolates have been recovered from humans during the 1999–2000 epidemics. If serum is to be tested for antibody only, it may be shipped or stored at ambient temperatures for up to 48 h, provided it is kept free of microbiologic contamination. Repeated freezing and thawing of samples may degrade antibody and should be avoided . Cross-reactions with other flaviviruses, including yellow fever, dengue, and members of the JE antigenic complex, limit the utility of the WNV ELISA. Some laboratories have established diagnostic ELISA absorbance ratios that compare reactivity to potentially cross-reacting flavivirus antigens. However, a 4-fold change in neutralizing antibody titer should still be sought to provide a specific diagnosis of WNV infection. Currently, commercial testing for WNV-specific antibody is limited, and because of the potential cross-reactions with antibodies to other flaviviruses, previous experience in performing and interpreting these tests is crucial. CDC-defined IgM

and IgG ELISAs that use specified antigens are preferred and performed by many States public health laboratories (13).

Treatment:

Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% in Romania (1996) to 12% in New York (1999) and 14% in Israel (2000) Case fatality rates have remained constant among U.S. patients in 2000 and 2001. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. For hospitalized persons older than 70 years of age, case fatality rates were 15% in Romania and 29% in Israel; in New York, persons 75 years of age and older were nearly nine times more likely to die than younger persons. Encephalitis with severe muscle weakness and change in the level of consciousness were also prominent clinical risk factors predicting death. Limited data suggest that certain preexisting conditions, such as diabetes mellitus or immunosuppression, may be independent risk factors for death. In one study of induced West Nile infections in patients with cancer, prolonged viremia and severe illness were more common among those with hematologic malignancies than among those with other types of cancer (14).

Prevention:

Clearly prevention is paramount in controlling the spread of this viral infection. Primary prevention in humans includes effective mosquito repellents (those containing DEET), avoiding locations where mosquitoes are biting, and barrier methods such as long sleeve clothing, long pants, and window screens. Additionally, active surveillance of the avian population by health departments and the reduction of mosquitoes through coordinated spraying of pesticides in highly populated mosquito areas are all strategies to help in the control of WNV. Although human vaccines for West Nile virus are under development , for the foreseeable future West Nile infection prevention will rest on two broad general strategies: 1) reducing the number of vector mosquitoes through actions taken by the public or by municipal authorities, 2) preventing vector mosquitoes from biting humans by using mosquito repellents; avoiding locations where vector mosquitoes are biting; and using barrier methods, such as window screens or long-sleeved clothing (15).

CONCLUSION:

Over the past decade, the understanding of the clinical spectrum of illness, as well as the immediate and longer-term outcomes associated with human WNV infection has increased substantially. However, there are remaining clinical questions that require further elucidation. Data on the long-term neurocognitive impact on patients recovering from WNE are scant, and further information is needed to ascertain long-lasting cognitive impairment following encephalitis from WNV. The parkinsonian features associated with acute WNV illness appear in most cases to be transient and resolve over time; however, recurrent- or early-onset parkinsonism in such patients due to the essence of dopaminergic neurons remains a hypothetical possibility. Similarly, whether patients recovering from WNP will develop recurrent limb weakness in previously affected limbs years after their acute illness, akin to ‘post-polio syndrome’ seen with poliovirus, is unknown at this point, but needs assessment. In the future, additional assessment of these and other clinical manifestations of WNV infection will be critical in aiding our understanding of the pathogenesis of WNV disease and hopefully will guide management and treatment options.

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