## Summary


- Flavivirus, belongs to JEV serogroup
- Vector: mosquito, Culex species
- Main clinical presentation: Febrile disease, neurological syndrome, (Arthralgia/ rash) (FD, NS, (AR))
- WNV neuroinvasive disease is an important clinical syndrome with up to 15% mortality and frequently accompanied by long-term sequelae


# Virus

West Nile Virus (WNV) was originally discovered in 1937 in the West Nile district of the Northern Province of Uganda. It belongs to the Flaviviridae. It belongs to the Japanese Encephalitis group flaviviruses (see section on Japanese Encephalitis). Kunjin virus is regarded as a variant of West Nile Fever Virus. There is a considerable variation between different strains (isolates).

# Transmission

WNV is transmitted by mosquitoes, mainly Culex species. Culex univittatus and C. pipiens are the main vectors in Africa and the Middle East. WNV has also been known to circulate Southern Europe (Romania, southern France, Spain), Israel, Asia, the Ukraine and Southern Russia. The main reservoir is probably formed by viraemic birds and a zoonotic mosquito-bird-mosquito cycle is assumed. Many bird varieties can be infected and can be viraemic for a long time (amplifying host). Since 1999 WNV has become endemic in the USA and Canada, where it demonstrates seasonality: 90% of infections occur in August and September.

One of the reasons why West Nile virus has spread so rapidly in the United States, is due to a hybrid mosquito species (Culex pipiens s.s. X Culex pipiens molestus), which bites both birds (ornithophilic) and man (anthropophilic). The infection usually takes a subclinical course in birds, but in an outbreak of West Nile Fever-like virus (afterwards confirmed as being West Nile Fever virus) in Queens in New York in the autumn of 1999 hundreds of birds in this city died from the infection (mainly crows, magpies and a few flamingos in the Bronx zoo). Prior to this the virus was unknown in the New World.

The infection is not transmitted directly from man-to-man, but it can be transmitted by blood transfusion, organ transplantation and breast feeding.

Kunjin virus occurs in Australia, Papua New Guinea (including Saibai island in the Torres Strait) and Borneo.

## Geographical distribution

Past epidemics occurred in South Africa in 1974 (with more than 3000 clinical cases), the Camargue (France) and the Ebro delta (Spain). From 1999 through 2010, 3 million WNV infections are thought to have occurred in the USA, resulting in 780 000 clinical illnesses. From 1999-2012 the USA have recorded 16,196 patients with WNV neuroinvasive disease and 1549 deaths.

## Clinical aspects

Incubation period varies from 3-15 days. Many infected patients experience a subclinical infection or a mild flu-like syndrome. Symptomatic patients present with headache, generalized weakness, morbilliform or maculopapular rash (often at time of defervescence), fever (often low grade, lasting 5 days on average), myalgia. Less commonly reported symptoms are joint pains, chills, painful eyes, vomiting or diarrhoea and lymphadenopathy.

**Table: Symptoms experienced by WNV viraemic blood donors in 14 days preceding donation**
**(Zou *et al*, J Infect Dis)**

| Symptom | No. (%) of donors with symptom |
|---|---|
| Headache[a] | 125 (75) |
| Generalized weakness[a] | 125 (75) |
| New rash[a] | 97 (58) |
| Fever[a] | 94 (56) |
| Severe muscle pain[a] | 90 (54) |
| Joint pain[a] | 81 (49) |
| Chills[a] | 79 (47) |
| Painful eyes[a] | 67 (40) |
| Vomiting or diarrhea | 45 (27) |
| Swollen glands | 36 (22) |
| Abdominal pain | 31 (19) |
| New difficulty thinking | 29 (17) |
| Bone pain | 27 (16) |
| Tremor | 4 (2) |

Neuroinvasive disease occurs in less than 1% of those infected by a mosquito bite and appears more frequent in elderly persons. The risk may approach 1 in 50 among persons aged at least 65 years, a rate 16 times higher than that for persons aged 16 to 24 years. In

addition, a history of cancer, diabetes, hypertension, alcohol abuse, or renal disease also increases the risk.

Other host factors associated with an increased risk of neuroinvasive disease are and chemokinereceptor CCR5 deficiency (which diminishes the risk for HIV infection) as well as male sex.

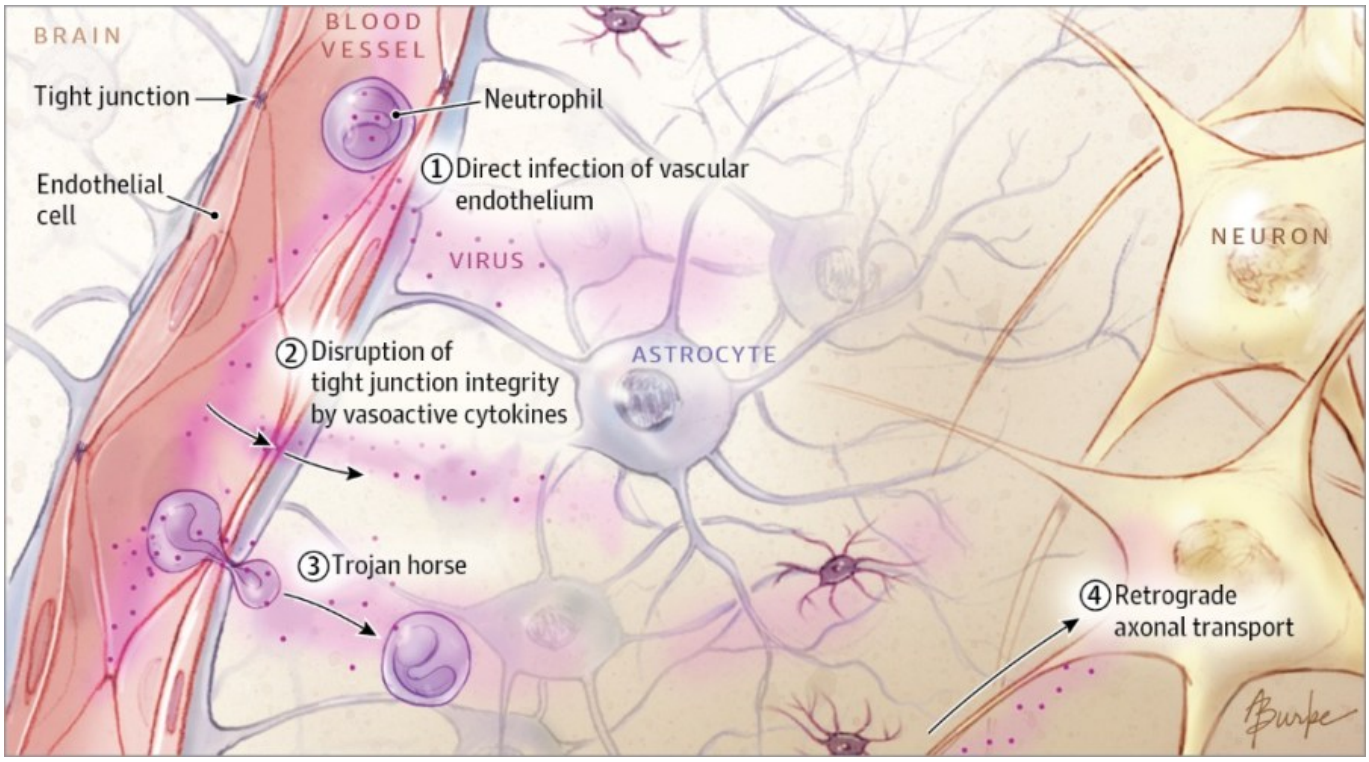



Figure: Potential mechanisms for neuroinvasion of West Nile virus (Petersen et al, JAMA)

**Mechanism of neuro invasion**

Neuroinvasive disease occurs in less than 1% of those infected by a mosquito bite and appears more frequent in elderly persons. Potential mechanisms for neuroinvasion of West Nile virus include (1) direct infection of the vascular endothelium and subsequent entry to the central nervous system, (2) viral passage through the vascular endothelium due to disruption of the blood-brain barrier integrity by vasoactive cytokines, (3) a Trojan horse mechanism through which infected monocytes are trafficked into the central nervous system, or (4) retrograde axonal transport to the central nervous system following infection

of peripheral neurons.

Reported clinical syndromes of WNV neuro-invasive disease are:

- Meningitis, characterized by clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photo- or phonophobia.
- Encephalitis characterized by depressed or altered level of consciousness, lethargy or personality change lasting more than 24 hours.
- Acute flaccid paralysis, characterized by acute onset of limb weakness with marked progression over 48 hours, which is usually asymmetric, areflexic or hyporeflexic, and without sensory abnormalities. 80% of acute flaccid paralysis cases occur in conjunction with encephalitis or meningitis.

Examination of CSF of patients with neuroinvasive disease shows normal glucose, elevated protein (generally <150 mg/dL) and moderate pleocytosis (generally <500 cells/µL) usually with a predominance of lymphocytes; however, neutrophils may predominate in early infection.

Imaging studies are usually normal, but focal lesions in the pons, basal ganglia, thalamus and anterior horns, and enhancement of the leptomeninges, the periventricular areas or both are occasionally seen. These lesions may appear hyperintense on T2-weighted magnetic resonance and fluid attenuated inversion recovery images.

The duration of WNV neuroinvasive disease is weeks to months; long-term functional and cognitive difficulties are common in these patients, but the number of quality studies (with adequate control groups) is low. The mortality rate is 0% in the unspecific flu-like syndrome, 2% in meningitis and up to 15% in the case of encephalitis.

## Diagnosis

West Nile virus is mostly diagnosed by detection of IgM antibody in serum or cerebrospinal fluid (CSF) by IgM antibody-capture ELISA (MAC-ELISA). Presence of anti-WNV IgM in CSF indicates CNS infection; it is found in 90% of patients with neuro-invasive disease within 8 days of symptom onset. However, anti-WNV IgM may not be detected in serum at clinical

presentation. Demonstration of seroconversion in a convalescent sample will provide a definitive diagnosis. Testing for IgG antibodies has no utility in the acute clinical diagnostic setting. Cross-reactivity with other flaviviruses can be distinguished by performing a plaque-reduction neutralization test (PRNT), but the test is only available in reference laboratories.

Nucleic acid amplification testing (eg. RT-PCR) is used in blood donor screening in the United States and Canada has nearly eliminated the risk of West Nile virus transfusion transmission. It also has utility in the diagnosis of WNV in symptomatic patients as an adjunct to MAC-ELISA. In a study of 276 WNV cases, 191 were tested by both serology and NAAT. Of these, 86 (45.0%), 111 (58.1%), and 180 (94.2%) were detected by NAAT, serology, and combined NAAT and serology, respectively. RT-PCR may prove useful to diagnose WNV in immunocompromised patients when antibody development is delayed or absent.

# Treatment

No antiviral treatment is available. Intravenous immunoglobulin (IVIG), West Nile virus–specific neutralizing monoclonal antibodies, corticosteroids, ribavirin, interferon α-2b, and antisense oligomers were not effective.

# Prevention

## Vaccination

In spite of 4 licensed equine vaccines and promising preliminary results from several phase 1 and 2 human vaccine candidates, phase 3 efficacy trials have not been attempted, probably because universal vaccination against WNV disease is unlikely to be cost-effective unless disease incidence increases substantially.

## Surveillance

Potentially epidemic conditions due to increased virus transmission can be monitored by regularly testing the blood of birds for the presence of the virus or antibodies. So-called “sentinel birds” are used for this. Crows are very sensitive to infection. Analysis of samples of dead crows is useful in the New World.

## Personal protection

The risk can be limited by reducing contact with mosquitoes. When there is an outbreak it is recommended that covering clothing is worn and that mosquito repellents are used. Insecticide can also be sprayed indoors. In the case of large epidemics, outdoor vector control is also important (larvicides and adulticides).