West Nile Virus

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Since its first North American case in 1999, West Nile Virus (WNV) has quickly established itself as an endemic disease of epidemic proportions (Gerber et al., 2004).

While the mode of migration from its native Africa is not understood, the virus that was first discovered in 1937 has now spread to Europe, Mexico, the Caribbean and is predicted to hit South America next year (Gould et al., 2004). WNV is carried by mosquitoes and birds, and through bites, is transmitted to humans. It cannot be passed between people without blood contact though there have been cases reported of people becoming infected through breast feeding, blood transfusions, as well as transplants, which necessitates better screening at blood donor clinics (Granwehr et al., 2004). There is currently no vaccine available, but there are many prospective vaccines undergoing clinical trials with results to be published shortly. Generally, the young and healthy are not at risk for developing serious illness or neurological disorders associated with WNV; however, the elderly and immunocompromised are at a significant risk for developing complications. Regardless, measures should be taken to avoid mosquito bites and control WNV (Granwehr et al., 2004).

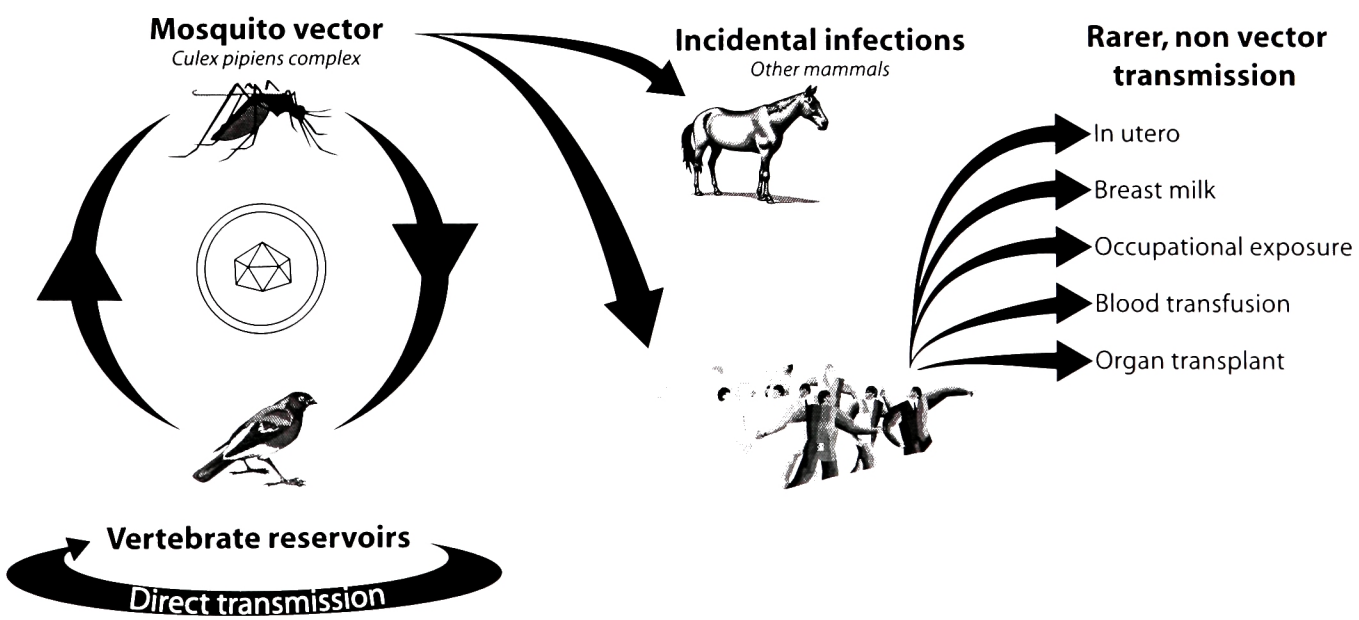

Figure 1: Typical West Nile Virus (WNV) life cycle (Gould et al., 2004).

Epidemiology

WNV is a single-stranded RNA flavivirus that, once in a host's blood stream, is able to replicate within the endoplasmic reticulum of vascular endothelial cells (Gerber et al., 2004; Brandt et al., 2004). WNV is maintained by a mosquito-bird-mosquito life cycle (Figure 1). Although this cycle is broken when other vertebrates are infected, the virus does not replicate enough to be transmitted further and the dead-end host becomes seriously ill (Gerber et al., 2004).

The virus was originally endemic in Africa and parts of Asia, but has quickly spread since the 1990's, introduced into new ecosystems through epidemics in Romania and North America (Gerber et al., 2004). It was originally hypothesized that the virus would die in the winter with most of the mosquito population. When the virus resurfaced in 2000, scientists found that it was harboured in the blood of Celux mosquitoes (Gould et al., 2004). The migration of birds continues to bring WNV further south. The number of infected birds increased tenfold between 2001 and 2002, and then again doubled in 2003 (Figure 2; Granwehr et al., 2004). Many subtypes of WNV have emerged since the outbreak in 1999, and the virus seems to be evolving throughout North America. This poses a severe threat, because the adaptations might render the virus more virulent.

While humans are considered dead-end hosts, several cases have occurred where the virus was transmitted between humans through breast milk, organ transplantation and blood transfusions. Blood transfusions and transplants are the most worrisome modes of transmission as only 20% of individuals exhibit symptoms, and the majority of WNV-infected donors will be unaware of their disease status (Granwehr et al., 2004). Between August 2002 and January 2003, 20 cases of WNV transmission through blood transfusion were reported, forcing the Food and Drug Administration to screen donors from April through November – the peak mosquito season (Granwehr et al., 2004). Even donors with WNV-like symptoms were deferred for 28 days, and those with symptoms after donating had to report to both the Centers for Disease Control and Prevention and the blood collection agency. The Food and Drug Association also insists on conducting nucleic acid tests before accepting donated blood to screen asymptomatic donors.

Signs and Symptoms

Few infected individuals exhibit symptoms, and of those, less than 1% develop neurological disease (Brandt et al., 2004). Symptoms range from a slight fever to severe neurological disease. Symptoms

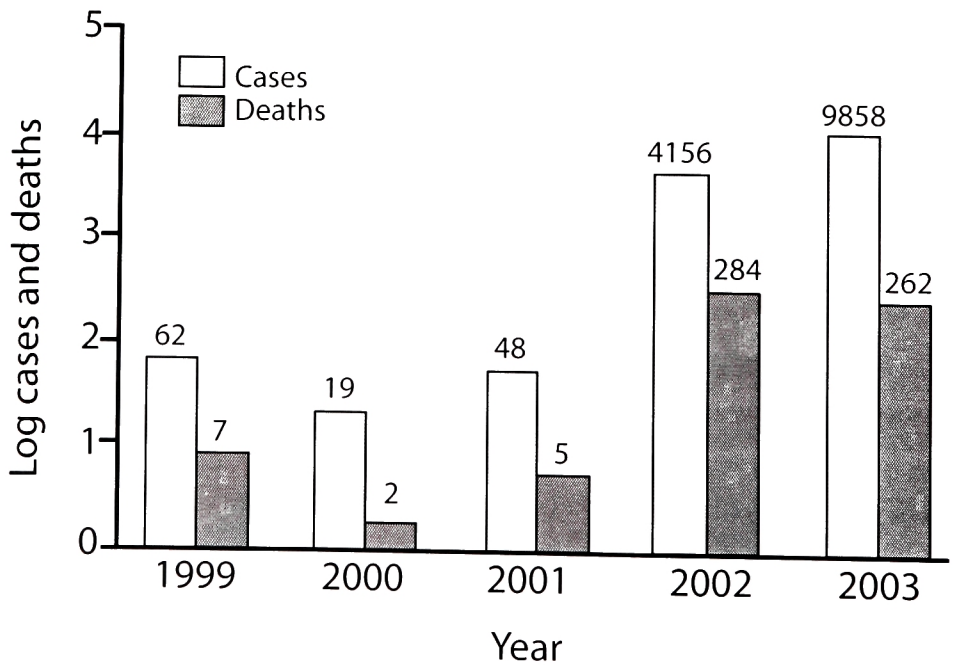

Figure 2: Human cases of West Nile Virus infection in the USA, 1999-2003. (Granwehr et al., 2004)

Clinical Criteria for assessment of patients with suspected West Nile Virus infection

West Nile Meningitis

Clinical signs of meningeal inflammation, including nuchal rigidity, Kerrig's or Brudzinski's sign, or photophobia. Other evidence of acute infection, including one or more of: fever (>38°C) or hypothermia (<35°C); cerebrospinal-fluid pleiocytosis (=5x10^9 leucocytes per L); peripheral leucocyte count > 10x10^9 per L; neuroimaging findings consistent with acute meningeal inflammation.

West Nile encephalitis

Encephalopathy (depressed or altered level of consciousness, lethargy, or personality change lasting at least 24 h.

Other evidence of CNS inflammation, including two or more of: fever (>38°C) or hypothermia (<35°C); cerebrospinal-fluid pleiocytosis (=5x10^9 leucocytes per L); peripheral leucocyte count > 10x10^9 per L; neuroimaging findings consistent with acute inflammation (with or without involvement of the meninges) or acute demyelination; presence of focal neurological deficit; evidence of meningeal inflammation; electroencephalography findings consistent with encephalitis; seizures, either new onset or exacerbation of previously controlled.

Acute flaccid paralysis

Acute onset of limb weakness with clear progression over 48 h. At least two of: asymmetry of weakness; areflexia/hporeflexia of affected limb(s); absence of pain, paraesthesia, or numbness in affected limb(s); cerebrospinal-fluid pleiocytosis (=5x10^6 leucocytes per L) and raised protein concentrations (=5x10^{6}mg/L); electrodiagnostic studies consistent with an anterior-horn-cell process; spinal-cord MRI documenting abnormal increased signal in the anterior grey matter.

Figure 3: Clinical criteria for assessment of patients with suspected WNV infection (Granwehr et al., 2004).

typically develop after an incubation period of 2 to 14 days (Brandt et al., 2004). West Nile Fever is the term used to describe symptomatic infection without any neurological disease. West Nile Fever is associated with malaise, nausea, vomiting, eye pain, headache, malagias and rashes, and lasts between 3 to 6 days (Granwehr et al., 2004). If the virus crosses the blood brain barrier, further neurological diseases arise and may result in death. These severe cases commonly occur in the immunocompromised and the elderly due to their decreased immunological capabilities (Granwehr et al., 2004). Hypertension is identified as a potential risk factor, as the endothelial walls deteriorate over time and allow the serum efficient access to areas of the brain (Granwehr et al., 2004). WNV infection of the central nervous system leads to three neurological disorders: encepahalitis, meningitis and acute flaccid paralysis (Figure 3; Granwehr et al., 2004). Encephalitis and meningitis are both life-threatening diseases caused by an inflammation of the brain and its lining, respectively. Acute flaccid paralysis resulting in asymmetric limb loss is less common (CDC, 2004).

Treatment

Once an individual is infected with WNV, the current practice is to assist the patient in fighting off the infection in the form of respiratory support, management of cerebral edema, and prevention of secondary bacterial infection (Gerber et al., 2004). Ribavirin, gamma-globulins, and steroids have all been suggested as treatment, but none have been subjected to clinical trials. In addition, interferon (an immuno-globulin) and ribavirin also demonstrate anti-WNV properties *in vitro*. However, the use of ribavirin in managing the WNV in Israel showed increased mortality (Brandt et al., 2004).

Immunoglobulins yield the most promising results. The US National Institute of Health recently sponsored a study to find effective ways of combating WNV with immunoglobulin therapy. Immunoglobulins serve as antibodies in the blood and are able to neutralize certain surface proteins on the premembrane of the virus (Granwehr et al., 2004). Intravenous immunoglobulins have been shown to decrease WNV populations in hamsters when administered within 24 hours of infection. Unfortunately, use of immunoglobulins would require active screening of people at risk and the late onset of WMV symptoms – typically beyond 24 hours – constrains the efficacy of this method of treatment (Gould et al., 2004). Currently, the available vaccines are ineffective for the general population. An equine vaccine made available in 2001 shows little effectiveness in humans, but there has since been some progress. The inactivated Japanese encephalitis virus and the yellow fever virus are being tested. However, these vaccines only reduce the severity of WNV infection.

Scientists believe that there are two viruses currently being studied that carry hope for future WNV vaccines. The first vaccine uses

a live-attenuated yellow fever 17D virus, termed Chimerivax, as a backbone. The vaccine is a hybrid of the premembrane and envelope protein genes of WNV and the non-structural genes of the 17D virus. Chimerivax was previously used to develop vaccines for yellow and dengue fevers (Granwehr et al., 2004). The vaccine prepares the body to deal with the infection before it occurs by exposing the immune system to the shell of the WNV virus. Upon second exposure, the immune system will produce the appropriate antibodies for the virus. The second virus being used in developing a WNV vaccine is a live dengue-4-chimeric virus containing the prM and E protein genes of WNV. This vaccine lowers mouse neurovirulence and neuroinvasiveness of wild-type WMV, and even protects the vaccinated organism from second exposure to WMV (Granwehr et al., 2004).

Prevention

Since vaccinations for WNV are not currently available, the only method of WNV prevention is to avoid mosquito bites. Even before applying insecticides or other chemicals in mosquito-infested areas, the most effective way of eliminating large populations of mosquitoes is to remove their breeding grounds – standing water. Cleaning out drain pipes, filling in standing water, and removing containers that may collect rainwater will greatly reduce the number of mosquitos (Gerber et al., 2004). In addition, securing screens around the house, using bed netting, applying mosquito repellent, and wearing low-exposure clothing outdoors are all effective ways of preventing mosquito bites (Brandt et al., 2004).

The most effective mosquito repellents contain a substance known as DEET. The concentration of DEET can range anywhere from 10-30%, with higher concentrations being more effective. However, DEET has been linked with adverse effects and should only be applied sparingly and be kept away from cut skin. To prevent ingestion of DEET by children, their hands should be washed immediately after outdoor activities (Gerber et al., 2004). Clothing treated with Pyrethroid, another class of insect repellent compounds, also reduces the rate of mosquito bites in a similar manner through mosquito repulsion and remains on clothing even after washing. Finally, use of bacterial and insect growth inhibitors can decrease the overall mosquito population in the community, thereby decreasing the number of bites. The most effective insecticides cause damage to the environment and will invariably kill other insects that are beneficial or crucial to the ecosystem (Brandt et al., 2004).

Conclusion

Since arriving in North America, WNV has spread to the Pacific Coast, Canada, Northern Mexico, and Jamaica. Although human cases have yet to be reported in these areas, steps must be taken to ensure that the absence of this virus is maintained (Granwehr et al., 2004). WNV has great potential to do harm in the elderly population, to blood transfusion recipients and to transplant recipients. It is time to realize that WNV has become endemic in North America with migrating bird populations that return from the South, further spreading the disease after every winter season. While certain vaccines may soon be developed and made available in hospitals, it is imperative that communities take action in preventing mosquito bites by adopting measures recommended by health experts.