flora

DERLEME/REVIEW

FLORA 2011;16(1):1-9

West Nile Virus Infections

Batı Nil Virüsü İnfeksiyonları

Zeliha KOÇAK TUFAN[1], Cemal BULUT[1]

[1] Clinic of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, Ankara, Turkey

SUMMARY

West Nile virus may cause a wide range of clinical presentations ranging from asymptomatic cases to fatal outcomes. Since it has been seen in Turkey and neighboring areas in recent years, it has attracted increased attention. The virus can cause West Nile fever and West Nile neuroinvasive disease, which includes meningitis, encephalitis and acute flaccid paralysis. Diagnosis is made by virus culture, polymerase chain reaction and ELISA. There is no specific therapy for West Nile virus infection and the principal therapy is mainly symptomatic.

Key words: *West Nile virus, Meningitis, Encephalitis*

ÖZET

Batı Nil Virüsü İnfeksiyonları

Zeliha KOÇAK TUFAN[1], Cemal BULUT[1]

[1] SB Ankara Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye

Batı Nil virüsü, asemptomatik infeksiyondan ölümcül seyreden ensefalite kadar farklı kliniklerle karşımıza çıkabilen, salgınlara neden olabilen bir virüstür. Son yıllarda Türkiye'de ve çevre ülkelerde yaz aylarında görülmeye başlanmış olması dikkatleri bu virüse çekmiştir. Virüs, Batı Nil ateşine ve menenjit, ensefalit ve akut flask paraliziyi içeren Batı Nil nöroinvaziv hastalıklarına neden olabilmektedir. Tanıda virüsün izolasyonu, polimeraz zincir reaksiyonu ve ELISA kullanılabilmektedir. Tedavide yeni gelişmeler olmakla birlikte spesifik bir tedavisi yoktur. Semptomatik ve destek tedavi esastır.

Anahtar Kelimeler: *Batı Nil virüsü, Ensefalit, Menenjit*

West Nile virus (WNV) is an arthropod-borne pathogen and is endemic in Asia, Europe and Africa. The virus was first isolated in 1937 in the West Nile region of Uganda. Since then, many outbreaks from different countries have been reported[1,2]. Because of the emerging disease in Turkey and neighboring regions in 2010 (Greece, Israel, Romania and Russia), the virus has attracted renewed and increased attention[3].

THE VIRUS

WNV is a single-stranded RNA virus belonging to the family Flaviviridae, genus *Flavivirus*. It is a mem-

Geliş Tarihi/Received: 04/02/2011 - Kabul Ediliş Tarihi/Accepted: 10/02/2011

ber of the Japanese encephalitis virus serogroup, which includes Japanese encephalitis (in Asia), Murray Valley encephalitis (in Australia), St. Louis encephalitis (in America) viruses, and Alfuy, Cacipacore, Koutango, Kunjin, Rocio, Stratford, Usutu and Yaounde viruses[1,2,4]. The virion consists of an envelope surrounding an icosahedral capsid of approximately 50 nm in size. The flavivirus life cycle consists of four principal stages: attachment/entry, translation, replication, and assembly/egress. Two domains are important in replication and virus protein processing: vesicle packets and convoluted membranes, respectively[5]. WNV enters cells via receptor-mediated endocytosis, and is transported into endosomes. The WNV receptor is unknown. A number of cell-surface proteins are potential WNV receptors (DC-SIGN, integrin alpha-v beta-3), and the receptor required for WNV binding and entry may vary by cell type[6-8].

EPIDEMIOLOGY

Mosquitoes, especially the genus *Culex*, are the principal vector of WNV. Wild birds are the principal host. Thus, the primary enzootic cycle for WNV is: mosquito-bird-mosquito[1,2,9,10]. Some of the wild birds suffer from high long-term viremia, which is critical for transmission to the vector mosquito. Humans and horses acquire the virus by mosquito bites, but the ensuing viremia is of low titer and short-lived and is insufficient for infecting other vector mosquitoes. Thus, humans and horses are accidental dead-end hosts but still may suffer from neurologic disease[1,2].

Since mosquito exposure is the primary route for transmission of WNV infection, activities related to this exposure, such as gardening or being outdoors at dusk or outdoors daily in endemic areas, are risk factors[11]. Older age and diabetes mellitus were found to be risk factors for developing neurologic disease[12-14].

The disease is usually seen during the summer and early fall (July to October)[12]. Unfortunately, the previous outbreaks and the resulting protective immunity cannot account for change in disease activity in humans. In affected countries, IgM seroprevalence ranges from 2% to 4%, and IgG seroprevalence ranges from 13% to 18%, a level that leaves most of the population susceptible to the disease[15,16]. The attack rate increases with increasing age[12].

After its discovery in 1937 in Uganda, several outbreaks have been reported from Israel, France, South Africa, North Africa, Russia, and the United States[1,2,12-14,17,18]. In the first outbreaks from Israel and South Africa, the mortality rate was low[19]. However, in 1996, many encephalitis cases and high mortality were reported from Romania[20]. This was the first outbreak of many that brought WN-associated diseases to the attention of the public and the medical community. In 1999, the virus reached the United States, and since then, WNV has been identified yearly in birds, mosquitoes and humans, with annual outbreaks involving thousands of people[4].

After its appearance in the United States and the countries in the Mediterranean basin in 2010, WNV infections drew attention in Turkey as well. According to the EpiSouth records, the first reported human cases from Turkey were from the Aegean and Marmara regions (Manisa, Sakarya, Izmir, Aydin and Isparta, Ministry of Health Reports 2010)[3] (Figure 1). There were 7 human cases, with 3 of them fatal[3]. Since the human cases of WNV infections were not detected before 2010, there have been limited studies about the seroprevalence of WNV in Turkey, most of which were performed in blood donors[21-27]. In a study conducted in 2006, WNV neutralizing antibodies were detected in several mammalian species from different provinces of Turkey, and the seroprevalence rates were found to be 13.5% in horses and 20.4% in humans[27]. Seroprevalence studies from healthy blood donors in central Anatolia and Ankara showed different WNV IgG positivity results: 0.56%, 1.6% and 2.4% in different studies[21,22,24]. However, similar studies from Southeast Turkey revealed higher seroprevalence rates, reaching as high as 16%[25,26].

TRANSMISSION

As mentioned above, the main transmission route is by mosquito bite. Although the *Culex* types are the main vector, *Aedes* and *Anopheles* types may also play a role in the transmission (Figure 2). There are other routes of transmission reported in the literature: blood transfusion, solid organ transplantation and percutaneous inoculation of laboratory workers[28-30]. A case report was defined for transplacental transmission, but a subsequent study on 74 pregnant women with WNV infection showed no transplacental transmission[31].

In 2002, 23 cases with blood transfusion from 16 donors developed WNV infection, but when the donors were investigated retrospectively, no antibody to WNV was detected[28]. After this outbreak, screening of blood donors for WNV by nuclear amplification tests was initiated in the United States and Canada.

In addition to the above-mentioned routes, ticks have also been shown to be able to transmit the virus in animal models[15].

WNV infected mosquitoes transmit the virus to humans following a blood-meal from the host. During this process, mosquito saliva contaminated with WNV is deposited in the blood and skin tissue. Virus contained within the skin is presumed to infect resident dendritic cells, and then goes to the draining lymph node[32,33]. Shortly thereafter, the virus amplifies in the tissues and results in a transient, low-level viremia, lasting a few days and typically waning with the production of anti-WNV IgM antibodies[34]. Following viremia, the virus infects multiple organs in the body of the host, including the spleen, liver and kidneys. Interestingly, 8 days after onset of symptoms, WNV was detected in the urine (viruria) of a patient with encephalitis, which is consistent with animal (hamster) experiments demonstrating viruria and the presence of viral infection in the kidneys[35,36].

CLINICAL and LABORATORY FINDINGS

The findings of the serologic studies showed that the majority (80%) of infected individuals are asymptomatic. The remaining symptomatic patients present with either West Nile fever (WNF) (20%) or West Nile neuroinvasive disease (WNND) (< 1%)[1,14]. WNND includes meningitis, encephalitis and acute flaccid paralysis (AFP). AFP is more commonly reported from North America than Europe[1-3].

Visual problems like blurry vision and photophobia are also reported in association with WNV infection. In addition, chorioretinitis, optic neuritis, vitreitis, and uveitis have also been reported[37-39]. Hepatitis and pancreatitis have been reported in cases of severe WNV infection[1].

1. West Nile Fever (WNF)

The disease is usually self-limited. Clinical disease generally occurs 2-6 days (range, 2-15 days) following the bite of an infected mosquito[4,10]. Fatigue is the most common symptom. Clinical features include fever, often accompanied by headache, malaise, myalgia, gastrointestinal symptoms like nausea, vomiting, abdominal pain, and diarrhea, and rash. Lymphadenopathy may be seen rarely[40]. The fever and headache usually last 5 days and 10 days, respectively. The rash is transient, nonpruritic, roseolar or maculopapular, and usually appears on the chest, back and arms, sparing the palms and soles. WNF is self-limited and is usually not fatal[40,41]. Difficulty with concentration, conjunctival congestion and pharyngitis may also be seen. Although the illness typically lasts 2-7 days, the duration of some of the symptoms such as fatigue may last up to 30 days[4,10,40].

2. West Nile Neuroinvasive Disease (WNND)

a. West Nile meningitis and encephalitis: The clinical findings are similar to those of WNF, plus headache and meningeal signs. Patients with headache and abnormal cerebrospinal fluid (CSF) findings are diagnosed as having meningitis. Patients with altered levels of consciousness or confusion, or who exhibit focal neurological signs, are diagnosed as having encephalitis. The distinction between these entities is clinical; some patients may exhibit mixed clinical signs and symptoms[1,2,9,10,13]. One of the differences is that WNV meningitis is usually seen in young adults (mean age 35), while encephalitis usually affects the elderly (mean age 70). Myoclonus, which is reported in about 30% of patients, occurs in the upper extremities and facial muscles. Parkinsonian features, including rigidity, bradykinesia and postural instability, are reported in up to 60% of patients[13,30,40]. Cranial nerve palsies, mainly of the seventh nerve, have been described as well. Seizures are reported less frequently[42]. Mortality from WNV infection was reported as approximately 8-14%, of which nearly all was attributed to West Nile encephalitis. The outcome is much worse in the elderly population, with mortality reaching as high as 30%[20,40,41].

b. Acute flaccid paralysis (AFP): AFP results from viral infection and damage to motor neurons in the anterior horn of the spinal cord. Asymmetric weakness and paralysis in one or more limbs can be seen but the sensory nerves are protected. Quadriplegia is also reported. Areflexia

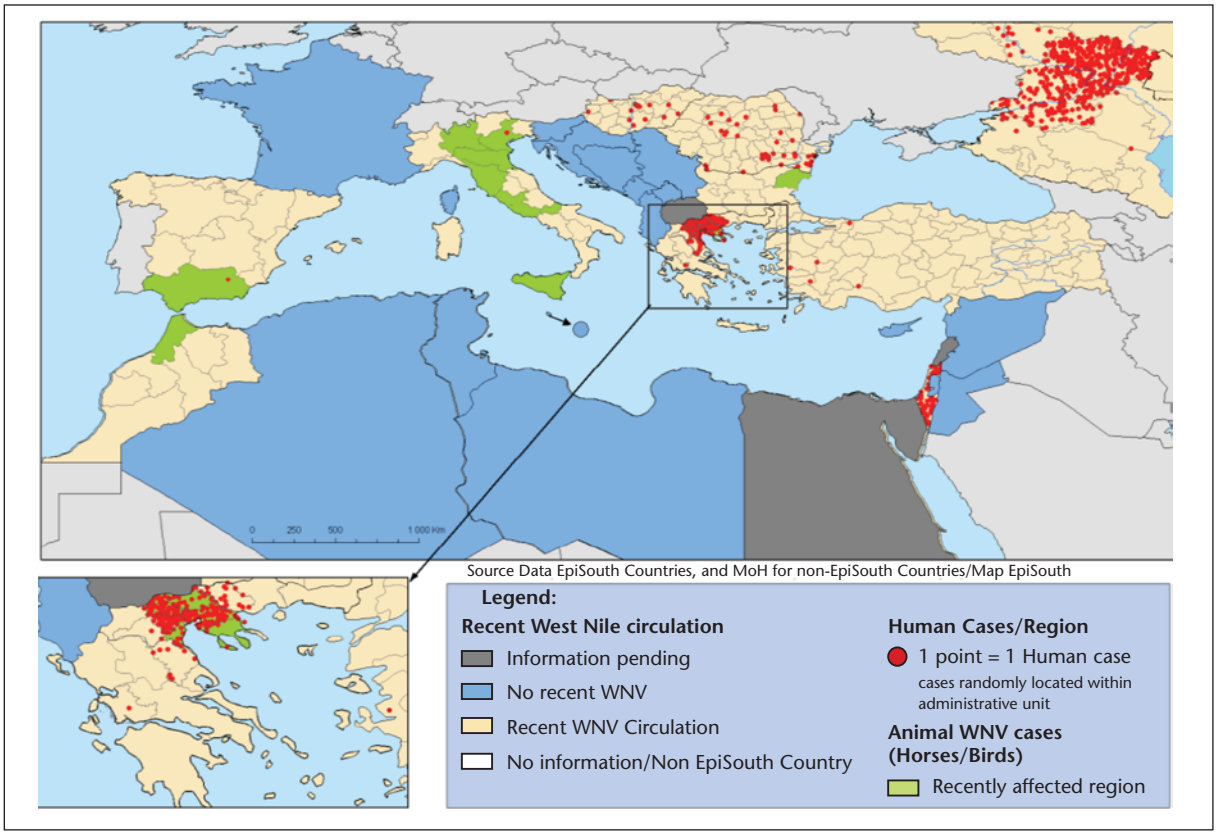

Figure 1. West Nile Circulation EpiSouth countries and neighbouring areas (Russia & Hungary).

or hyporeflexia and loss of bowel and bladder function can also occur. AFP generally develops early in the course of the disease, and can accompany either encephalitis or meningitis[1,2]. Diagnostic tests including CSF examination should be performed in order to differentiate WNV infection from stroke, myopathy and Guillain-Barré syndrome. Other clinical symptoms may include tremor, myoclonus, postural instability, bradykinesia, and signs of Parkinsonism[5].

Laboratory Findings

Anemia and leukocytosis (40%) and thrombocytopenia (15%) may be seen in patients with WNV infection. Hyponatremia (35-50%), hypokalemia (13%) and liver function abnormalities (20%) are also reported in the literature[1]. In meningitis cases, the CSF findings are similar to those of viral meningitis.

In encephalitis cases, electroencephalography (EEG) may be performed. EEG patterns are characterized by diffuse, nonspecific slow wave abnormalities, consistent with encephalitis. In one study, anterior predominance of slow waves was found to be characteristic in WNV infection[43].

In AFP-suspected cases, electromyelography (EMG) and nerve conduction studies have to be done. Motor axonopathy, along with preservation of sensory nerve potentials, could be found on EMG. These tests can be normal in the first 2 weeks of the disease[1].

Computed tomography findings are usually normal. Magnetic resonance imaging is also usually normal in the initial days of the disease, but the frequency of abnormal lesions increases over the first week and even later. When present, lesions can be found in deep gray matter structures, predominantly the posterior thalami and basal ganglia[13,44].

DIAGNOSIS

The clinical signs and symptoms are not specific and one has to be suspicious of WNV infection to make the correct diagnosis. Endemic areas must con-

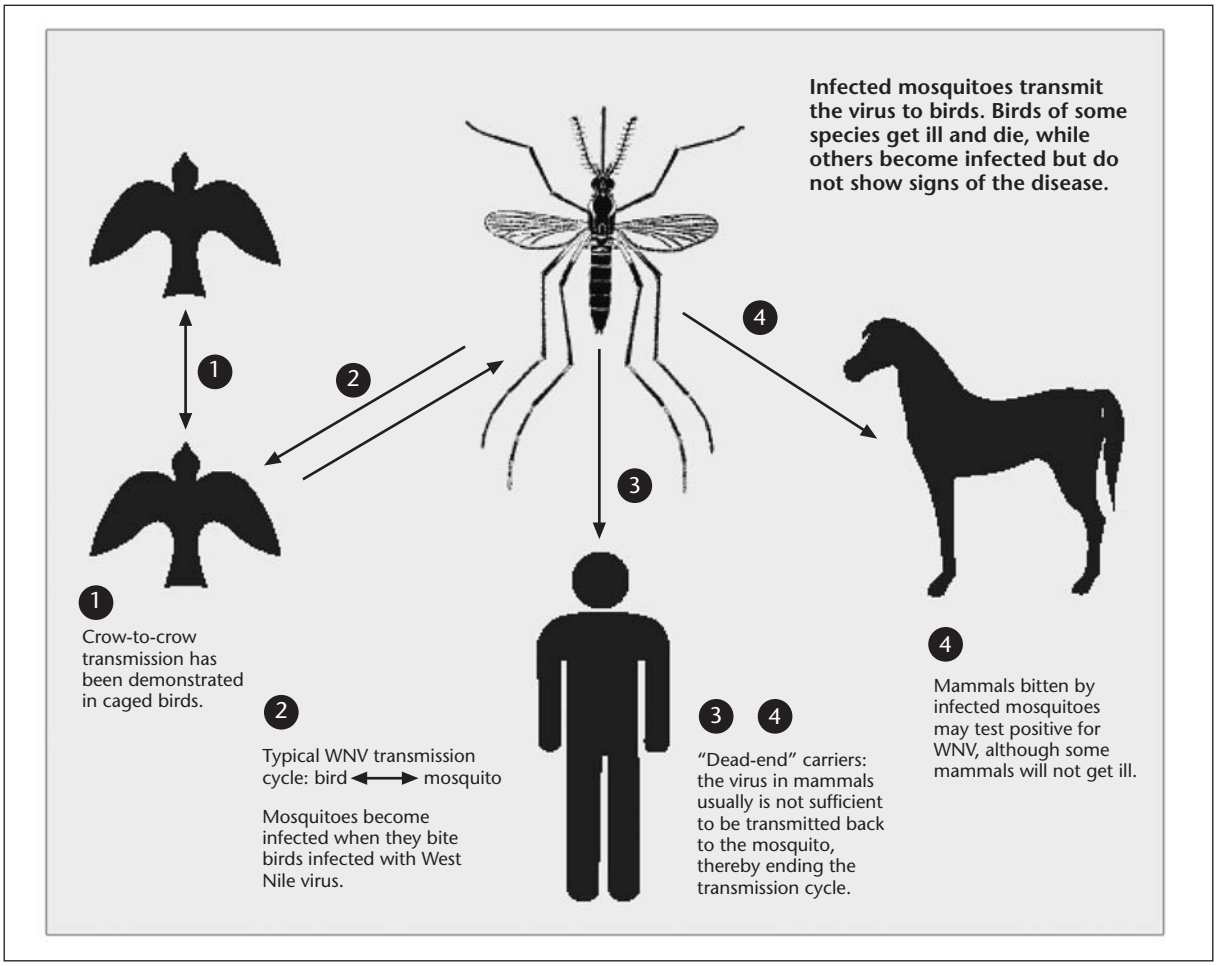

Figure 2. Transmission of the West Nile virus (Center for Biologic Counterterrorism and Emerging Diseases CBC-ED).

sider WNV infection, especially during the summer months. Isolation of the virus from the blood by culture is the gold standard. However, viremia is not long-lasting in WNV infections, and the virus can be recovered from the blood only in the first few days of the disease[2]. Following viremia, the virus infects multiple organs in the body of the host, including the spleen, liver and kidneys. Interestingly, 8 days after onset of symptoms, WNV was detected in the urine (viruria) of a patient with encephalitis, which is consistent with the presence of viral infection in the kidneys[36,45].

The routine use of virus culture is limited to high-level laboratories or to some national laboratories. Thus, serology is the most widely used diagnostic tool in many places. Diagnosis is made by detecting IgM antibodies in the blood or CSF or by observing a four-fold increase in IgG or IgM titer between acute and convalescent samples taken 10 to 28 days apart[1,5]. After an acute WNV infection, approximately 50% of patients are expected to have persistent IgM antibodies for more than 8 months, and in a few patients, IgM antibodies persisted for over a year[46]. Thus, the presence of IgM antibody alone is not diagnostic of acute WNV infection, and a four-fold rise in antibody titer is required for confirmation. Moreover, cross-reacting antibodies can emerge either from infection or from vaccination with other flaviviruses, such as St. Louis encephalitis, Japanese encephalitis, dengue, or yellow fever[5].

The polymerase chain reaction (PCR) is a very specific test, but it lacks acceptable sensitivity. In a

study that compared diagnosis with PCR to serology, PCR had low sensitivity (57-70%)[1].

CASE DEFINITION

According to the Centers for Disease Control and Prevention (CDC) guidelines published in 2003, the case classification is as follows[10]:

A clinically compatible illness, *plus*:

Confirmed case:

1. Four-fold or greater change in WNV-specific serum antibody titer,

2. Isolation of WNV from or demonstration of specific WN viral antigen or genomic sequences in tissue, blood, CSF, or other bodily fluid, or

3. WNV-specific IgM antibodies demonstrated in serum by antibody-capture enzyme immunoassay and confirmed by demonstration of WNV-specific serum neutralizing antibodies in the same or a later specimen.

Probable case: WNV-specific serum IgM antibodies detected by antibody-capture enzyme immunoassay but with no available results of a confirmatory test for WNV-specific serum neutralizing antibodies in the same or a later specimen.

THERAPY

Unfortunately, there is no specific treatment available for WNV infections. In severe cases, treatment consists of supportive care that involves hospitalization and supportive therapy like intravenous fluids, respiratory support and prevention of secondary infections. Attention to the level of consciousness and airway protection are critical[1,47]. Although there is no proven specific treatment, various drugs have been used in some of the outbreaks, and several clinical trials are also ongoing[47].

The antiviral drug ribavirin was found to inhibit WNV grown in tissue culture[48]. However, in another report from the Israeli outbreak, ribavirin was given to patients with WNND and was found to be correlated with higher mortality. Possible explanations for this unexpected finding are that sicker patients were preferentially treated and that subtherapeutic doses of ribavirin were administered[1].

One of the clinical trials is based on interferon IFN-α2b (CDC info). IFN-α2b was found to be effective in murine models when administered before WNV challenge, but not after viral exposure[49].

Human immunoglobulin (immunoglobulin with high titer against WNV) was found to be effective in treating WNV-infected mice when administered before or right after inoculation, during the viremic phase before the virus has entered the brain[50]. It is not clear, however, whether this approach is relevant to humans, who are usually diagnosed after the disappearance of viremia and the beginning of WNND.

There is also a controlled trial testing the drug MGAWN1 for the treatment of WNV infections, but the results are not yet available[51]. Another study published in 2010 suggested that cyclooxygenase (COX)-2 inhibitors modulate WNV-induced COX-2 and prostaglandin E2 signalling, so they may have potential in the clinical management of neuroinflammation associated with WNV[52]. A very recent study showed that valproic acid, a drug used for neurologic disorders, inhibited multiplication of all the enveloped viruses tested, including the zoonotic lymphocytic choriomeningitis virus and WNV[53].

Intravenous immunoglobulin (IVIG) has also been used in some cases and showed promising results. WNV appears to be more susceptible to antibody-mediated than cell-mediated immunity, and animal models have demonstrated that passive transfer of specific antibodies abort or ameliorate WNV infections in a dose-dependent manner[54]. Several animal studies have demonstrated that immunoglobulin has the greatest benefit when administered before the development of neurological symptoms, whereas the role of administering immunoglobulin after symptom onset is less clear[55,56]. The first successful use of IVIG in human WNV infection was reported in 2000, when a woman with chronic lymphocytic leukemia became comatose from WNV encephalitis and recovered after IVIG treatment[57]. Several successful outcomes associated with IVIG treatment have subsequently been reported in immunocompromised patients, including lung and renal transplant recipients in 2000 and 2005; both patients had severe neuroinvasive WNV disease, but recovered fully after prompt administration of IVIG[58,59]. One case with AFP due to WNV infection was successfully treated with IVIG from Israeli donors[60]. IVIG contains a high titer of anti-WNV antibodies (1/1600). Recently, OMRIX Biopharmaceuticals of Israel developed a strategy for the selection of plasma units from the 10%

fraction of blood donors containing WNV antibodies. Positive units were processed into the pharmaceutical grade WNV IVIG (WNIG). WNIG is at least 5- to 10-fold more potent than regular Israeli IVIG[54]. There is also a case in the literature who had WNV infection after solid organ transplantation who was treated successfully with IVIG[61].

PREVENTION

WNV infection is transmitted by mosquitoes. Thus, reduced exposure to mosquitoes is the best method of protection. Because the vectors, the *Culex* mosquitoes, are night feeders, protection is needed from dusk to dawn. A comprehensive mosquito eradication program should be a priority in endemic countries[1].

In the absence of effective treatment, vaccination against WNV infection is attractive. There is an equine vaccine, but unfortunately no human vaccine against WNV is currently available[1,2].

Here are the CDC recommendations for prevention[62]:

• Education about reducing the risk of infection is important for all persons in transmission areas, but especially in the higher-risk populations (persons more than 50 years old and those who are immunocompromised).

• The primary prevention step recommended is the use of mosquito repellent when outdoors. Mosquitoes may bite through thin clothing, so spraying clothes with repellent containing permethrin or DEET will give extra protection. These repellents are the most effective and the most studied.

• The more DEET a repellent contains the longer it can protect from mosquito bites. DEET concentrations higher than 50% do not increase the length of protection.

• Repellents containing permethrin are not approved for direct application on the skin. Repellent containing DEET should not be sprayed on the skin under clothing. For detailed information about using repellents, see "Insect Repellent Use and Safety" (www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm).

• Other options include wearing protective clothing (long sleeves, socks, and long pants) when outdoors.

• The primary mosquito-biting hours for many of the species that are important vectors of WNV are from dusk to dawn. It is advisable to either stay indoors during these hours or use protective clothing and repellent.

• Household mosquito-source reduction is also important. Standing water should be removed from outdoor receptacles in the peri-residential environment.

• Integrated mosquito management can be another important factor in controlling mosquito populations (See "Q & A: Pesticides Used in Mosquito Control": www.cdc.gov/ncidod/dvbid/westnile/qa/pesticides.htm).

REFERENCES

1. *Chowers M. West Nile fever. In: Schwartz E (ed). Tropical Diseases in Travelers. 1st ed. Singapore: Blackwell Publishing, 2009:65-73.*
2. *Green S, Rothman AL. West Nile virus. In: Gorbach SL, Bartlett JG, Blacklow NR (eds). Infectious Diseases. 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2004:2128-32.*
3. *West Nile virus circulation in the EpiSouth countries and neighbouring areas (Hungary and Russia) Update 6th of October 2010. Accessed: 22 March 2011. Available from: http://www.episouth.org*
4. *West Nile virus. Information and guidance for clinicians. Accessed: 20 March 2011. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/clinicians/pdf/wnv-epidemiology-clinguidance.pdf*
5. *Rossi SL, Ross TM, Evans JD. West Nile virus. Clin Lab Med 2010;30:47-65.*
6. *Chu JJ, Ng ML. Interaction of West Nile virus with alpha v beta 3 integrin mediates virus entry into cells. J Biol Chem 2004;279:54533-41.*
7. *Chu JJ, Ng ML. Infectious entry of West Nile virus occurs through a clathrin-mediated endocytic pathway. J Virol 2004;78:10543-55.*
8. *Medigeshi GR, Hirsch AJ, Streblow DN, Nikolich-Zugich J, Nelson JA. West Nile virus entry requires cholesterol-rich membrane microdomains and is independent of alphavbeta3 integrin. J Virol 2008;82:5212-9.*
9. *West Nile Fever. European Centre for Disease Prevention and Control. Accessed: 10 March 2011. Available from: http://www.ecdc.europa.eu/en/healthtopics/west_nile_fever/Pages/index.aspx*
10. *Epidemic/Epizootic West Nile Virus in the United States: Guidelines for Surveillance, Prevention and Control. Accessed: 10 March 2011. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/resources/wnv-guidelines-aug-2003.pdf*

11. *Han LL, Popovici F, Alexander JP Jr, Laurentia V, Tengelsen LA, Cernescu C, et al. Risk factors for West Nile virus infection and meningoencephalitis, Romania, 1996. J Infect Dis 1999;179:230-3.*
12. *Tsai TF, Popovici F, Cernescu C, Campbell GL, Nedelcu NI. West Nile encephalitis epidemic in southeastern Romania. Lancet 1998;352:767-71.*
13. *Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al; 1999 West Nile Outbreak Response Working Group. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med 2001;344:1807-14.*
14. *Chowers MY, Lang R, Nassar F, Ben-David D, Giladi M, Rubinshtein E, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. Emerg Infect Dis 2001;7:675-8.*
15. *Serter D. Flaviviruslar. In: Willke Topçu A, Söyletir G, Doğanay M (editörler). Enfeksiyon Hastalıkları ve Mikrobiyolojisi. İstanbul: Nobel Tıp Kitabevleri, 2008:1737-8.*
16. *Chowers MY, Green MS, Bin H, Weinberger M, Schlaeffer F, Pitlik S, et al. Post-epidemic serosurvey of West Nile fever in Israel. Eur J Clin Microbiol Infect Dis 2005;24:851-3.*
17. *Weinberger M, Pitlik SD, Gandacu D, Lang R, Nassar F, Ben David D, et al. West Nile fever outbreak, Israel, 2000: epidemiologic aspects. Emerg Infect Dis 2001;7:686-91.*
18. *Hayes EB, Komar N, Nasci RS, Montgomery SP, O'Leary DR, Campbell GL. Epidemiology and transmission dynamics of West Nile virus disease. Emerg Infect Dis 2005;11:1167-73.*
19. *Dauphin G, Zientara S, Zeller H, Murgue B. West Nile: worldwide current situation in animals and humans. Comp Immunol Microbiol Infect Dis 2004;27:343-55.*
20. *Cernescu C, Ruta SM, Tardei G, Grancea C, Moldoveanu L, Spulbar E, et al. A high number of severe neurologic clinical forms during an epidemic of West Nile virus infection. Rom J Virol 1997;48:13-25.*
21. *Ayturan S, Aydoğan S, Ergünay K, Ozcebe OI, Us D. Investigation of West Nile virus seroprevalence in Hacettepe University Hospital blood donors and confirmation of the positive results by plaque reduction neutralization test. Mikrobiyol Bul 2011;45:113-24.*
22. *Hızel K, Yenicesu I, Erdal B, Yeşilyurt E, Fidan I, Kalkancı A, et al. Investigation of West Nile virus seroprevalence in healthy blood donors. Mikrobiyol Bul 2010;44:425-30.*
23. *Ergünay K, Aydoğan S, Menemenlioğlu D, Sener B, Lederer S, Steinhagen K, et al. Investigation of West Nile virus in central nervous system infections of unknown etiology in Ankara, Turkey. Mikrobiyol Bul 2010;44:255-62.*
24. *Ergünay K, Saygan MB, Aydoğan S, Menemenlioğlu D, Turan HM, Ozkul A, et al. West Nile virus seroprevalence in blood donors from Central Anatolia, Turkey. Vector Borne Zoonotic Dis 2010;10:771-5. Epub 2009 Dec 20.*
25. *Ozer N, Ergünay K, Simsek F, Kaynas S, Alten B, Caglar SS, et al. West Nile virus studies in the Sanliurfa Province of Turkey. J Vector Ecol 2007;32:202-6.*
26. *Ergunay K, Ozer N, Us D, Ozkul A, Simsek F, Kaynas S, et al. Seroprevalence of West Nile virus and tick-borne encephalitis virus in southeastern Turkey: first evidence for tick-borne encephalitis virus infections. Vector Borne Zoonotic Dis 2007;7:157-61.*
27. *Ozkul A, Yildirim Y, Pinar D, Akcali A, Yilmaz V, Colak D. Serological evidence of West Nile Virus (WNV) in mammalian species in Turkey. Epidemiol Infect 2006;134:826-9. Epub 2005 Nov 29.*
28. *Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med 2003;349:1236-45.*
29. *Iwamoto M, Jernigan DB, Guasch A, Trepka MJ, Blackmore CG, Hellinger WC, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med 2003;348:2196-203.*
30. *Centers for Disease Control and Prevention (CDC). Laboratory-acquired West Nile virus infections-United States, 2002. MMWR 2002;51:1133-5.*
31. *Centers for Disease Control and Prevention (CDC). Intrauterine West Nile virus infection-New York, 2002. MMWR 2002;51:1135-6.*
32. *Byrne S, Halliday GM, Johnston LJ, King NJ. Interleukin-1 beta but not tumor necrosis factor is involved in West Nile virus-induced Langerhans cell migration from the skin in C57BL/6 mice. J Invest Dermatol 2001;117:702-9.*
33. *Johnston L, Halliday GM, King NJ. Langerhans cells migrate to local lymph nodes following cutaneous infection with an arbovirus. J Invest Dermatol 2000;114:560-8.*
34. *Busch MP, Kleinman SH, Tobler LH, Kamel HT, Norris PJ, Walsh I, et al. Virus and antibody dynamics in acute West Nile virus infection. J Infect Dis 2008;198:984-93.*
35. *Tesh RB, Siirin M, Guzman H, Travassos da Rosa AP, Wu X, Duan T, et al. Persistent shedding of West Nile virus in urine of experimentally infected hamsters. Am J Trop Med Hyg 2005;72:320-4.*
36. *Ding X, Wu X, Duan T, Siirin M, Guzman H, Yang Z, et al. Nucleotide and amino acid changes in West Nile virus strains exhibiting renal tropism in hamsters. Am J Trop Med Hyg 2005;73:803-7.*
37. *Hershberger VS, Augsburger JJ, Hutchins RK, Miller SA, Horwitz JA, Bergmann M. Chorioretinal lesions in nonfatal cases of West Nile virus infection. Ophthalmology 2003;110:1732-6.*
38. *Kuchtey RW, Kosmorsky GS, Martin D, Lee MS. Uveitis associated with West Nile virus infection. Arch Ophthalmol 2003;121:1648-9.*
39. *Sampson BA, Ambrosi C, Charlot A, Reiber K, Veress JF, Armbrustmacher V. The pathology of human West Nile virus infection. Hum Pathol 2000;31:527-31.*

40. *Watson JT, Pertel PE, Jones RC, Siston AM, Paul WS, Austin CC, et al. Clinical characteristics and functional outcomes of West Nile fever. Ann Intern Med 2004;141:360-5.*
41. *Asnis DS, Conetta R, Waldman G, Teixeira AA. The West Nile virus encephalitis outbreak in the United States (1999-2000): from Flushing, New York, to beyond its borders. Ann N Y Acad Sci 2001;951:161-71.*
42. *Leis AA, Stokic DS, Webb RM, Slavinski SA, Fratkin J. Clinical spectrum of muscle weakness in human West Nile virus infection. Muscle Nerve 2003;28:302-8.*
43. *Gandelman-Marton R, Kimiagar I, Itzhaki A, Klein C, Theitler J, Rabey JM. Electroencephalography findings in adult patients with West Nile virus-associated meningitis and meningoencephalitis. Clin Infect Dis 2003;37:1573-8.*
44. *Carson PJ, Konewko P, Wold KS, Mariani P, Goli S, Bergloff P, et al. Long-term clinical and neuropsychological outcomes of West Nile virus infection. Clin Infect Dis 2006;43:723-30.*
45. *Tonry JH, Xiao SY, Siirin M, Chen H, da Rosa AP, Tesh RB. Persistent shedding of West Nile virus in urine of experimentally infected hamsters. Am J Trop Med Hyg 2005;72:320-4.*
46. *Shi PY, Wong SJ. Serologic diagnosis of West Nile virus infection. Expert Rev Mol Diagn 2003;3:733-41.*
47. *West Nile Virus: Treatment Information and Guidance for Clinicians. Accessed: 10 March 2011. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/clinicians/pdf/wnv-treatment-clinguidance.pdf*
48. *Jordan I, Briese T, Fischer N, Lau JY, Lipkin WI. Ribavirin inhibits West Nile virus replication and cytopathic effect in neural cells. J Infect Dis 2000;182:1214-7.*
49. *Morrey JD, Day CW, Julander JG, Blatt LM, Smee DF, Sidwell RW. Effect of interferon-alpha and interferon-inducers on West Nile virus in mouse and hamster animal models. Antivir Chem Chemother 2004;15:101-9.*
50. *Ben-Nathan D, Lustig S, Tam G, Robinzon S, Segal S, Rager-Zisman B. Prophylactic and therapeutic efficacy of human intravenous immunoglobulin in treating West Nile virus infection in mice. J Infect Dis 2003;188:5-12.*
51. *Treatment of West Nile Virus with MGAWN1 (PARADIGM). Accessed: 20 March 2011. Available from: http://clinicaltrials.gov/ct2/show/NCT00927953*
52. *Verma S, Kumar M, Nerurkar VR. Cyclooxygenase-2 inhibitor blocks the production of West Nile virus-induced neuroinflammatory markers in astrocytes. J Gen Virol 2011;92:507-15.*
53. *Vázquez-Calvo A, Saiz JC, Sobrino F, Martín-Acebes MA. Inhibition of enveloped virus infection of cultured cells by valproic acid. J Virol 2011;85:1267-74.*
54. *Ben-Nathan D, Gershoni-Yahalom O, Samina I, Khinich Y, Nur I, Laub O, et al. Using high titer West Nile intravenous immunoglobulin from selected Israeli donors for treatment of West Nile virus infection. BMC Infect Dis 2009;9:18.*
55. *Diamond MS, Shrestha B, Marri A, Mahan D, Engle M. B cells and antibody play critical roles in the immediate defense of disseminated infection by West Nile encephalitis virus. J Virol 2003;77:2578-86.*
56. *Jackson AC. Therapy of West Nile virus infection. Can J Neurol Sci 2004;31:131-4.*
57. *Shimoni Z, Niven MJ, Pitlick S, Bulvik S. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. Emerg Infect Dis 2001;7:759.*
58. *Hamdan A, Green P, Mendelson E, Kramer MR, Pitlik S, Weinberger M. Possible benefit of intravenous immunoglobulin therapy in a lung transplant recipient with West Nile virus encephalitis. Transpl Infect Dis 2002;4:160-2.*
59. *Saquib R, Randall H, Chandrakantan A, Spak C, Barri Y. West Nile encephalitis in a renal transplant recipient: the role of intravenous immunoglobulin. Am J Kidney Dis 2008;52:19-21.*
60. *Walid MS, Mahmoud FA. Successful treatment with intravenous immunoglobulin of acute flaccid paralysis caused by west nile virus. Perm J 2009;13:43-6.*
61. *Rhee C, Eaton EF, Concepcion W, Blackburn BG. West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature. Transpl Infect Dis 2011. doi: 10.1111/j.1399-3062.2010.00595.x [Epub ahead of print]*
62. *West Nile Virus: prevention Information and Guidance for Clinicians http://www.cdc.gov/ncidod/dvbid/westnile/clinicians/pdf/wnv-prevention-clinguidance.pdf*

Yazışma Adresi/Address for Correspondence

Dr. Zeliha KOÇAK TUFAN

SB Ankara Eğitim ve Araştırma Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği
06340 Ulucanlar, Ankara-Türkiye

E-posta: drztufan@yahoo.com