INFORMATION AND GUIDANCE FOR CLINICIANS

West Nile Virus: Clinical Description

West Nile Fever

- **Most persons who become infected with West Nile virus (WNV) develop no clinical illness or symptoms.** In previous outbreaks in the Northern Hemisphere, an estimated 80% of people who became infected with WNV never developed symptoms attributable to the infection.
- **Of the approximately 20% of infected people who do develop symptoms, most develop what has been termed West Nile fever.**
- **The incubation period for WNV infection is thought to range from about 2 to 14 days**, although longer incubation periods have been documented in immunosuppressed persons.

Clinical Features of West Nile Fever

- Fever
- Headache
- Fatigue
- Skin rash on the trunk of the body (occasionally)
- Swollen lymph glands (occasionally)
- Eye pain (occasionally)

Severe Disease: West Nile Meningitis, West Nile Encephalitis, and West Nile Poliomyelitis

- **When the central nervous system (CNS) is affected, clinical syndromes ranging from febrile headache to aseptic meningitis to encephalitis may occur**, and these are usually indistinguishable from similar syndromes caused by other viruses.
- **About 60% to 75% of people with neuroinvasive WNV infection reportedly have encephalitis or meningoencephalitis**, which is characterized by altered mental status or focal neurologic findings.
- **About 25% to 35% of people with neuroinvasive WNV infection reportedly have meningitis without evidence of encephalitis.**
- **Headache can be a prominent feature of WNV fever, meningitis, or encephalitis and is not a useful indicator of neuroinvasive disease.**
- **West Nile meningitis usually involves fever, headache, and stiff neck.** Pleocytosis is present. Changes in consciousness are not usually seen and are mild when present.

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- **West Nile encephalitis, the most severe form of neuroinvasive West Nile viral disease, involves fever and headache, but there are more global symptoms.** There is usually an alteration of consciousness, which may be mild and result in lethargy but may progress to confusion or coma. Focal neurologic deficits, including limb paralysis and cranial nerve palsies, may be observed. Tremors and movement disorders also have been noted.

- **West Nile poliomyelitis, a flaccid paralysis syndrome associated with WNV infection, is less common than meningitis or encephalitis.** This syndrome is generally characterized by the acute onset of asymmetric limb weakness or paralysis in the absence of sensory loss. Pain sometimes precedes the paralysis. The paralysis can occur in the absence of fever, headache, or other common symptoms associated with WNV infection. Involvement of respiratory muscles, leading to acute respiratory failure, can sometimes occur. For more information, see "Q & A: WNV Poliomyelitis" (www.cdc.gov/ncidod/dvbid/westnile/qa/poliomyelitis.htm).

Clinical Features of Severe Disease

- Fever
- Gastrointestinal symptoms
- Ataxia and extrapyramidal signs
- Optic neuritis
- Seizures
- Weakness
- Change in mental status
- Myelitis
- Polyradiculitis
- A minority of patients with severe disease develop a maculopapular or morbilliform rash involving the neck, trunk, arms, or legs.
- Flaccid paralysis is sometimes seen.
- Although not observed in recent outbreaks, myocarditis, pancreatitis, and fulminant hepatitis have been described.

Common Laboratory Findings of Severe Disease

- Total leukocyte counts in peripheral blood is mostly normal or elevated with lymphocytopenia and anemia also occurring.
- Hyponatremia is sometimes present, particularly among patients with encephalitis.
- Examination of the cerebrospinal fluid (CSF) shows pleocytosis, usually with a predominance of lymphocytes. Protein is universally elevated. Glucose is normal.
- Computed tomography is not useful in the diagnosis of WNV infection, but is useful in excluding other etiologies of acute meningoencephalitis. Brain MRI is often normal, but will sometimes display leptomeningeal enhancement or parenchymal signal changes."

Diagnostic Tests for Severe Disease

- WNV infection can be suspected in a person based on clinical symptoms and patient history. Laboratory testing is required for a confirmed diagnosis.
- The most efficient diagnostic method is detection of IgM antibody to WNV in serum collected within 8 to 14 days of illness onset or CSF collected within 8 days of illness onset using the IgM antibody-capture, enzyme-linked immunosorbent assay (MAC-ELISA).
- Since IgM antibody does not cross the blood-brain barrier, presence of IgM in CSF strongly suggests central nervous system infection. Patients who have been recently vaccinated against or

recently infected with related flaviviruses (e.g., yellow fever, Japanese encephalitis, dengue) may have positive WNV MAC-ELISA results, although vaccination or non-CNS infections should not give CSF IgM, and killed vaccines (e.g., JE-VAX) should not produce IgM at all.

- One caveat is that serological tests for WN virus cross react with other closely related flaviviruses (Japanese encephalitis, St. Louis encephalitis, yellow fever, dengue). Neutralization assays (plaque reduction neutralization tests) are more specific and should be considered if any of these other infections are suspected.
- The plaque-reduction neutralization test (PRNT), the most specific test for the arthropod-borne flaviviruses, can be used to help distinguish false-positive results in an IgM antibody-capture enzyme-linked immunosorbent assay or other assays (for example, indirect immunofluorescence and hemagglutination inhibition). The plaque-reduction neutralization test may also help distinguish serologic cross-reactions among the flaviviruses, although some degree of cross-reaction in neutralizing antibody may still cause ambiguous results, especially if the current infection is not the first flavivirus infection the patient ever experienced. Because most infected persons are asymptomatic and because IgM antibody may persist for six months or longer, residents in endemic areas may have persistent IgM antibody from a previous infection that is unrelated to their current clinical illness.
- There are cross-reactivity issues with the neutralizing antibody test as well.
- PCR is used in the diagnosis of WNV infections in humans, although it has limited usefulness because of the transient and low viremias. With PCR, WNV genetic material can be detected in CSF in up to 50% of patients who present with acute West Nile meningoencephalitis. Because this is not a very good sensitivity, a negative test does not rule out a WNV infection. Serology should be used in these patients.
- Virus culture is the gold standard, but it is rarely positive except in autopsy material, generally from the brain and other solid organs.
- Serum or CSF can be refrigerated or frozen if submitting samples to a reference laboratory for testing for WNV.
- Autopsy specimens can be subjected to a variety of tests for detecting the presence of WNV: PCR tests on fresh-frozen material, virus culture on fresh-frozen material, and histology and immunohistochemistry on formalin-fixed tissue.
- A significant increase in WNV–specific neutralizing antibody titer between acute- and convalescent-phase serum specimens confirms acute infection. These additional tests require growth of the virus and may take a week or longer (plus shipping time) to conduct.
- The CT scan has not been effective in identifying any signs that are consistent or unique for WNV encephalitis in particular or for flaviviral encephalitis in general. MRI is more effective but will yield abnormal results in only 25% to 35% of cases, and the MRI abnormalities are nonspecific.

Clinical Suspicion

- The diagnosis of WNV infection relies on a high index of clinical suspicion and on results of specific laboratory tests.
- WNV or other arboviral diseases, such as St. Louis encephalitis, should be seriously considered in adults 50 years of age or older who have onset of unexplained encephalitis or meningitis in late summer or early fall.
- The local presence of WNV enzootic activity or other human cases of WNV infection should further raise the index of suspicion.
- Severe neurologic disease due to WNV infection has occurred in persons of all ages, and because year-round transmission is possible in southern states, WNV should always be considered in persons with unexplained encephalitis and meningitis.

- Before sending diagnostic specimens to CDC, please consult the "Instructions for Sending Diagnostic Specimens for Serology Testing by the DVBID Arbovirus Diagnostic Laboratory" (www.cdc.gov/ncidod/dvbid/misc/arboviral_shipping.htm).

Related Links

- "Q & A: Symptoms of WNV" (www.cdc.gov/ncidod/dvbid/westnile/qa/symptoms.htm)
- "Q & A: Testing and Treating WNV in Humans" (www.cdc.gov/ncidod/dvbid/westnile/qa/testing_treating.htm)
- "Laboratory Diagnosis" (Section 2 from "Epidemic/Epizootic West Nile Virus in the United States: Guidelines for Surveillance, Prevention, and Control"): www.cdc.gov/ncidod/dvbid/westnile/resources/wnv-guidelines-aug-2003.pdf