Arboviral Diseases (Neuroinvasive and Non-Neuroinvasive)

Merlin reporting code = 06250 California serogroup Virus Neuroinvasive Disease
= 06251 California serogroup Virus Non-Neuroinvasive Disease
= 06220 Eastern Equine Encephalitis Neuroinvasive Disease
= 06221 Eastern Equine Encephalitis Non-Neuroinvasive Disease
= 06230 St. Louis Encephalitis Neuroinvasive Disease
= 06231 St. Louis Encephalitis Non-Neuroinvasive Disease
= 06620 Venezuelan Equine Encephalitis Neuroinvasive Disease !
= 06621 Venezuelan Equine Encephalitis Non-Neuroinvasive Disease !
= 06630 West Nile Virus Neuroinvasive Disease
= 06631 West Nile Virus Non-Neuroinvasive Disease
= 06210 Western Equine Encephalitis Neuroinvasive Disease
= 06211 Western Equine Encephalitis Non-Neuroinvasive Disease
= 06000 Arboviral Disease, Other
Case report form (CRF): *Florida Confidential Vector-borne Disease Infection CRF*
MERLIN EXTENDED DATA REQUIRED

Background

Arthropod-borne viruses (arboviruses) are transmitted to humans primarily through the bites of infected mosquitoes, ticks, sand flies, or midges. Other modes of transmission for some arboviruses include blood transfusion, organ transplantation, perinatal transmission, breastfeeding, and laboratory exposures.

More than 130 arboviruses are known to cause human disease. Most arboviruses of public health importance belong to one of three virus genera: *Flavivirus*, *Alphavirus*, and *Orthobunyavirus*.

Clinical description

Most arboviral infections are asymptomatic. Clinical disease ranges from mild febrile illness to severe encephalitis. Other clinically compatible symptoms of arbovirus disease may include headache, myalgia, rash, arthralgia, vertigo, vomiting, paresis, altered mental status, seizures, limb weakness, or nuchal rigidity. For the purposes of surveillance and reporting, based on their clinical presentation, arboviral disease cases are often categorized into two primary groups: neuroinvasive disease and non-neuroinvasive disease.

Neuroinvasive disease

Many arboviruses cause neuroinvasive disease such as aseptic meningitis, encephalitis, or acute flaccid paralysis (AFP). These illnesses are usually characterized by the acute onset of fever with headache, myalgia, stiff neck, or cerebrospinal fluid (CSF) pleocytosis (increase in WBC count). AFP may result from anterior ("polio") myelitis, peripheral neuritis, or post-infectious peripheral demyelinating neuropathy (i.e., Guillain-Barré syndrome). Less common neurological manifestations, such as cranial nerve palsies, also occur.

Non-neuroinvasive disease

Most arboviruses are capable of causing an acute systemic febrile illness (e.g., West Nile fever) that may include headache, myalgia, arthralgia, rash, or gastrointestinal symptoms. Some viruses also can cause more characteristic clinical manifestations, such as severe polyarthralgia or arthritis due to chikungunya, Zika, Mayaro, Ross River, and O'nyong-nyong viruses.

Clinical criteria for case classification

Clinically compatible illness for arboviral disease is defined as follows:

Neuroinvasive disease
An illness characterized by both of the following:
- Meningitis with an increase in WBCs in CSF (pleocytosis), encephalitis, AFP, or other acute signs of central or peripheral neurologic dysfunction, as documented by a physician AND
- Absence of a more likely clinical explanation.

Non-neuroinvasive disease
An illness characterized by all the following:
- Fever (chills) as reported by the patient or a health care provider;
- Absence of neuroinvasive disease, AND
- Absence of a more likely clinical explanation.

Laboratory criteria for case classification

Confirmatory:
Neuroinvasive
- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in tissue, blood, **CSF**, or other body fluid (e.g., culture, immunohistochemistry [IHC], or polymerase chain reaction [PCR]);

OR
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera (e.g., enzyme-linked immunosorbent assay [EIA/ELISA], microsphere immunoassay [MIA], or immunofluorescence assay [IFA]);

OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen (e.g., EIA/ELISA with serum neutralization [SN] or plaque reduction neutralization [PRNT]);

OR
- Virus-specific IgM antibodies (e.g., EIA/ELISA, MIA, or IFA) in CSF with our without a reported pleocytosis, and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.

Non-neuroinvasive disease
- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, or other body fluid, **excluding CSF**,

OR
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera,

OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen.

Presumptive:
Neuroinvasive and non-neuroinvasive disease
- Virus-specific IgM antibodies (e.g., EIA/ELISA, MIA, or IFA) in serum but with no other testing for arboviruses endemic to the region where exposure occurred.

Neuroinvasive disease only
- Virus-specific IgM antibodies (e.g., EIA/ELISA, MIA, or IFA) in CSF but with no other testing for arboviruses endemic to the region where exposure occurred.

Note that in Florida, West Nile virus (WNV) and St. Louis encephalitis virus (SLEV) are endemic and testing should be performed for both viruses. Dengue EIA/ELISA or PCR is recommended in non-neuroinvasive disease cases to rule out local dengue introductions. Chikungunya testing may also be recommended for some non-neuroinvasive disease cases.

Case classification

Confirmed:

Neuroinvasive disease

Illness clinically compatible with neuroinvasive disease in a person with confirmatory laboratory evidence.

Non-neuroinvasive disease

Illness clinically compatible with non-neuroinvasive disease in a person with confirmatory laboratory evidence.

Probable:

Neuroinvasive disease

Illness clinically compatible with neuroinvasive disease in a person with presumptive laboratory evidence.

Non-neuroinvasive disease

Illness clinically compatible with non-neuroinvasive disease in a person with presumptive laboratory evidence.

Comments

Interpreting arboviral laboratory results

- **Serologic cross-reactivity.** In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely related arboviruses occur, serologic testing for more than one virus may be needed and results compared to determine the specific causative virus. For example, such testing might be needed to distinguish antibodies resulting from infections (or vaccinations) within genera, e.g., flaviviruses such as West Nile, St. Louis encephalitis, Powassan, dengue, yellow fever, or Japanese encephalitis viruses.
- **Rise and fall of IgM antibodies.** For most arboviral infections, IgM antibodies are generally first detectable at 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented (e.g., up to 500 days for West Nile virus). Serum collected within 8 days of illness onset may not have detectable IgM and testing should be repeated on a convalescent-phase sample to rule out arboviral infection in those with a compatible clinical syndrome.
- **Persistence of IgM antibodies**. Arboviral IgM antibodies may be detected in some patients months or years after their acute infection, particularly WNV. Therefore, the presence of these virus-specific IgM antibodies may signify a past infection and be unrelated to the current acute illness. Finding virus-specific IgM antibodies in CSF or a fourfold or greater change in virus-specific antibody neutralizing titers between acute- and convalescent-phase serum specimens provides additional laboratory evidence that the arbovirus was the likely cause of the patient's recent illness. Clinical and epidemiologic history also should be carefully considered.
- **Persistence of IgG and neutralizing antibodies**. Arboviral IgG and neutralizing antibodies can persist for many years following a symptomatic or asymptomatic infection. Therefore, the presence of these antibodies alone is only evidence of previous infection and clinically compatible illnesses with the presence of IgG, but not IgM, should be evaluated for other etiologic agents with the exception of some dengue infections. In addition, a virus neutralization test (SN or PRNT) is required to differentiate virus specific IgG within the flavivirus family although commercial

laboratories often incorrectly report IgG results for a specific flavivirus. For instance, EIA results reported as positive for WNV IgG antibody should actually be reported as being positive for flavivirus antibody IgG.

- **Other information to consider**. Vaccination history, detailed travel history, date of onset of symptoms, and knowledge of potentially cross-reactive arboviruses known to circulate in the geographic area should be considered when interpreting results.
- **Differentiating between dengue and West Nile infections in patients with positive flavivirus labs**
  - WNV IgM titers are negative or low positive in dengue fever patients (or vice versa); however the WNV IgG can be quite elevated in dengue patients since IgG strongly cross-reacts between flaviviruses.
  - Neuroinvasive disease is relatively uncommon with dengue infections and more likely to be WNV infection than dengue. Confusion differentiating WNV and dengue infections is most likely in patients without symptoms of neuroinvasive disease (fever patients).
  - Travel to a dengue endemic country in the 2 weeks prior to febrile illness onset or travel of a household member to a dengue endemic country in the 4 weeks prior to patient illness should increase suspicion of dengue.
  - Joint pain is often much more severe in cases of dengue fever compared to WNV fever.
  - Thrombocytopenia and leukopenia are more common in cases of dengue fever compared to WNV fever.

Imported arboviral diseases

Human disease cases due to dengue, chikungunya, or yellow fever viruses are nationally notifiable to CDC using specific case definitions. However, many other exotic arboviruses (e.g., Zika, Japanese encephalitis, tick-borne encephalitis, Venezuelan equine encephalitis, and Rift Valley fever viruses) are important public health risks for the U.S. as competent vectors exist that could allow for sustained transmission upon establishment of imported arboviral pathogens. Health-care providers and public health officials should maintain a high index of clinical suspicion for cases of potentially exotic or unusual arboviral etiology, particularly in international travelers. If a suspected case occurs, it should be reported to the appropriate local/state health agencies and CDC. Arboviral encephalitis cannot be distinguished clinically from other central nervous system (CNS) infections.

Acute and convalescent sera from reported cases must be sent to the Bureau of Public Health Laboratories for confirmatory testing.

Notes

For the most recent Surveillance and Control of Selected Arthropod-borne Diseases in Florida Guidebook and additional information about arboviral diseases, please visit: http://www.floridahealth.gov/%5C/diseases-and-conditions/mosquito-borne-diseases/index.html.

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