

West Nile Encephalitis

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CASE:

The patient is a 58 y/o Caucasian male who presented with his wife to the emergency department with a chief complaint of "I'm sick." The patient stated that 5 days prior to presentation, he felt feverish, with a maximum temperature measured at home of 101.5 °F as well as feeling malaise, that he states is only getting worse, which was his main concern in seeking emergency treatment. The patient also complained of a diffuse headache and neck stiffness. He had referred pain down to his lower back when he touched his chin to his chest. The patient stated, also, that he developed a diffuse rash 3 days prior to presentation on his right bicep that became diffuse, started resolving 1 day prior, and now he only had it on his shins. The patient affirms to nausea, but denied any vomiting, denied diarrhea, cough, sore throat, chest pain, shortness of breath, calf pain or swelling, abdominal pain, arthralgias, myalgias, ataxia, dizziness, focal weakness, urinary habit changes, anxiety or depression. Patient denied any recent travel or sick contacts. The patient's wife stated that she didn't notice anything different about him other than him being very ill.

The patient denied any past medical history, surgical history, psychiatric history, or family history. The patient denied any smoking history, illicit drug abuse, and stated that he only consumed 1-2 drinks of alcohol at social events. The patient worked as a janitor at an institution that cared for severely mentally disabled people. The patient denied any allergies to foods or medications and denied taking any regular medications other than over the counter medicines for his fever, which he took Aspirin 325 mg orally just prior to arrival.

The patient's vital signs on arrival were blood pressure 122/69 mm Hg, heart rate 95 bpm, respiratory rate 18 bpm, and temperature orally was 97.9 °F, pulse oximetry was 97% on room air. The patient was awake, alert, and oriented to time, place, and purpose and appeared uncomfortable, fatigued, and ill. Physical exam showed: head was normal cephalic and atraumatic, extraocular muscles were intact with white sclera and normal conjunctiva, otoscopic exam did not show evidence of pathology, ophthalmoscopic exam did not show any evidence of papilledema, retinal vasculature abnormalities, mucous membranes were dry and tacky, neck had normal range of motion, no jugular venous distention, was non-tender and no meningeal signs were appreciated. Chest exam was clear to auscultation, no rales, rhonchi or wheezes. Cardiovascular exam showed heart sounds were regular rate and rhythm with no gallops, rubs, or murmurs and +2/4 bilateral radial and dorsalis pedis pulses. Abdominal exam was non-tender, non-distended, with bowel sounds in all four quadrants and no signs of peritonitis. Back exam was non-tender with no costo-vertebral angle tenderness. Both of the upper extremities and lower extremities showed no evidence of edema, cyanosis, or clubbing of digits. The pre-tibial region of both legs had a pinpoint, flat, non-blanching, non-pruritic rash.

The patient's metabolic panel showed a glucose 114, sodium 135, potassium 3.9, chloride 99, co2 29, creatinine 1.12, BUN 14, calcium 9, magnesium 2.1, and phosphorus 3.8. The complete blood count showed a WBC 5.7, RBC 5.46, Hemoglobin 17.2, Hematocrit 50.4, Platelets 159 with a normal differential. Liver Function Tests showed a total bilirubin of 1.6, indirect bilirubin 1.4, total protein 6.4, ALT 19, AST 17. CRP was negative. Urine Drug Screen and EtOH levels were all negative. Urinalysis was

negative. Rapid Strep was negative. Lumbar puncture showed the following: Glucose 61 (normal range 40-70), Protein 68 (normal range 15-45), Tube #1 showed a color of red with WBC 4,750 and RBC of 2,750. Tube #3 showed a colorless fluid with WBC of 0 and RBC of 16. Gram Stain negative for any organisms. The CSF differential showed 20% neutrophils, 66% lymphocytes, and 11% monocytes.

It was at this point that a consult was placed in the emergency department for Infectious Disease. Upon consult, the patient presentation and results were discussed with the infectious disease fellow who discussed the case with the ID attending physician on call. The consult was placed for the appearance of aseptic meningitis, but there was confusion due to the difference in cell counts between Tube #1 and Tube #3. In discussing the case with ID, it was determined to be aseptic meningitis secondary to a viral etiology, and there was no indication for admission and antibiotic treatment. The difference in cell counts was likely due to a traumatic tap initially, which cleared by Tube #3. Since the patient was stable, he was discharged to home and follow-up with infectious disease as an outpatient. Additional orders were sent for further CSF analysis, which included fluid culture, Lyme titer, Arbovirus, Enterovirus, and West Nile virus. The patient was discharged with strict instructions of when and where to follow up and also reasons to return to the emergency department. The patient was discharged with a diagnosis of aseptic meningitis.

REVISIT:

The patient returned to the emergency department 2 days later, sent in from the Infectious Disease office. After re-evaluating the results of the original lumbar puncture and following the patient for 2 days who appeared to be having worsening symptoms, the ID attending wanted the patient to have a repeat lumbar puncture to re-evaluate the CSF for possible bacterial meningitis and subsequent antibiotic treatment. The CSF fluid's WBC count was corrected for the RBC's, which one can do if there is suspicion of a traumatic tap, and it still showed a significant number of white blood cells. The patient stated this time in the ED that he was still having persistent fevers and diffuse headache, not relieved by ibuprofen or acetaminophen, and the rash and neck stiffness had completely resolved. The patient also complained of nausea and photophobia. Per the wife, since leaving the ED 2 days prior, the patient has "just not been himself" with increasing confusion (not knowing where he was at times), having trouble finding words, and at times, slurring his speech. The patient was also seen having difficulty with ambulation, having to lean on the wall to keep his balance.

The patient's vital signs were a blood pressure of 142/78 mm Hg, heart rate of 78 bpm, respirations were 24 bpm, temperature was 102.8 °F, and pulse oximetry was 95% on room air. The patient was awake, alert, and oriented to time, place, and purpose and appeared comfortable, fatigued, and ill. Pertinent findings on physical exam included normal range of motion of the neck in sidebending, rotation, flexion, extension, with negative kernig and brudzinski signs. A punctate maculopapular rash was found on both wrists and ankles. No neurological deficits were noted.

The patient's complete blood count, electrolytes, renal function tests, glucose, coagulation profile, and cardiac profile were all within normal limits. The patient's EKG showed normal sinus rhythm at 72 bpm, normal axis, a non-specific interventricular conduction delay, and no abnormal ST-T abnormalities. The chest x-ray was negative. The repeat urinalysis was negative. The repeat CT of the brain was negative. Repeat CSF analysis showed: Glucose 67 (normal range 40-70), Protein 82 (normal range 15-45), Tube #3 showed a hazy fluid with WBC of 77 and RBC of 24. Gram Stain negative for any organisms with few white blood cells seen. The CSF differential showed 10% neutrophils, 75% lymphocytes, and 15% monocytes.

ADMISSION:

Infectious Disease was called for consult once results returned from this second ER visit. The results were discussed, and again, ID urged CSF be sent for analysis of RPR, HSV1 PCR, West Nile Virus PCR which was completed again on the repeat lumbar puncture. The patient was admitted to telemetry under the general internal medicine service and would be seen in consult by infectious disease and neurology. To cover for herpes encephalitis, the patient was started on acyclovir 1 gram IV every 8 hours and ceftriaxone 1 gram every 12 hours. For possible tick borne illness, doxycycline 100 mg oral twice daily was started. For possible bacterial illness, vancomycin 1 gram every 12 hours was begun as well. Supportive care with intravenous fluids and antibiotic treatment would continue until further information was provided. Neurology consult was obtained and recommended MRI of brain with and without contrast, as this is better for evaluating encephalitis. No additional recommendations were made at this time.

During admission, additional test results began returning. Blood cultures were negative. Urine cultures were negative. Throat cultures were negative. Sputum cultures were negative. CSF fluid cultures were negative. CSF results that returned while the patient was still in the hospital included negative IgM and IgG antibodies to cytomegalovirus, lyme, and coxsackie A and B. Rocky Mountain Spotted Fever (ricketsia) and VDRL were both negative as well. The MRI of the patient's brain with and without contrast showed significant motion artifact, but no gross acute abnormalities. An EEG was then obtained which was resulted as mildly abnormal due to global slowing and diffuse theta activity which can be seen with infection, toxic metabolic encephalitis, or medications. The patient was kept in the hospital for 5 days. The patient had a benign hospital course with improvement in his mentation, ambulation, and overall wellbeing. He was discharged to sub-acute rehabilitation with acyclovir 1 gram orally three times a day for one week, doxycycline 100 mg orally twice a day for one week, and levetiracetam 750 mg orally three times a day for seizure prophylaxis secondary to encephalitis, and given a follow-up appointment with infectious disease in one week.

The CSF serology results that returned approximately 1.5 weeks after the initial emergency department presentation showed all of the following to be negative: Eastern Equine IgG and IgM, California Encephalitis IgG and IgM, St. Louis Encephalitis IgG and IgM, Western Equine IgG and IgM. The Echovirus Antibodies (4,7,9,11,30) were negative. West Nile IgG was negative. And finally, West Nile IgM was **POSITIVE**.

APPROACH:

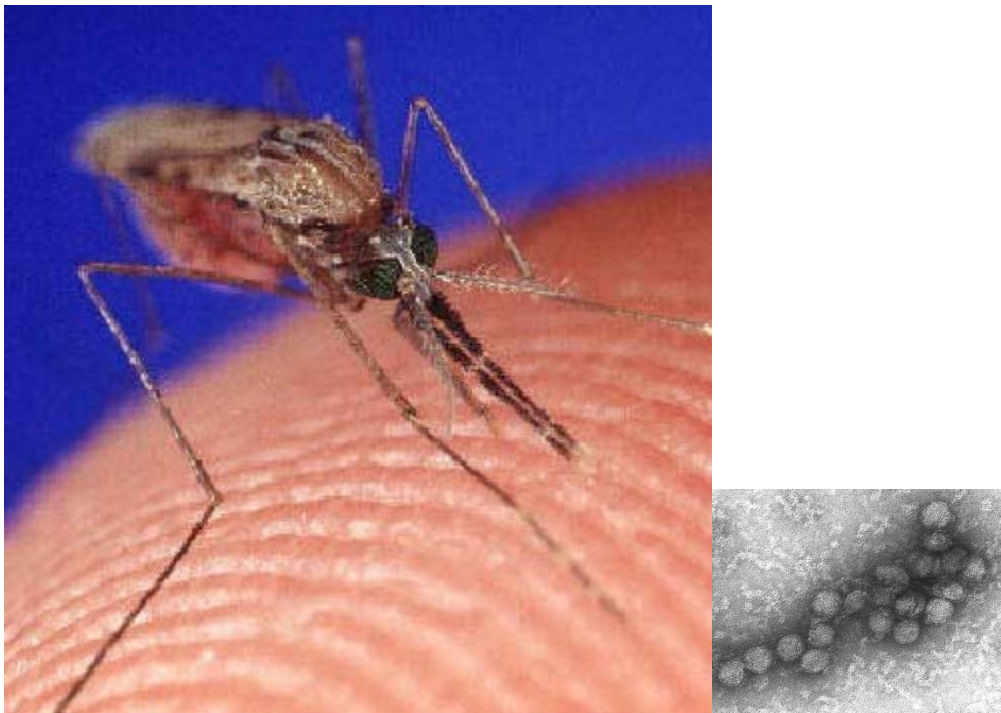
Acute infections of the nervous system are among the most important problems in medicine because early recognition can be life-saving. These infections include acute bacterial meningitis, viral meningitis, encephalitis, and focal infections of the brain such as brain abscess, subdural empyema, or infectious thrombophlebitis. Each presents with non-specific symptoms of fever and headache which may initially be thought to be benign, until the patient develops altered consciousness, focal neurological signs, or seizures.

Distinguishing between an infection involving the subarachnoid space (meningitis) or whether there is a generalized or focal area of the brain affected is the first task. Nuchal rigidity is a pathognomonic sign of meningeal irritation and presents as neck resistance with passive flexion. Kernig's sign is elicited with the patient in the supine position when the thigh is flexed on the abdomen with the knee flexed and attempts at passively extending the knee elicits pain with meningeal irritation. Brudzinkski's sign is elicited with the patient in the supine position and is positive when passive flexion

of the neck results in spontaneous flexion of the hips and knees. Both Kernig's and Brudzinski's sign have unknown sensitivity and specificity, and may even be absent in meningitis in the very young and very old patient population, immunocompromised, or patients with severely depressed mental status.

Empirical therapy should be started promptly in anyone with a high suspicion of bacterial meningitis. All patients should have CT or MRI of the brain prior to lumbar puncture. Patients with recent head trauma, immunocompromised states, have known malignant lesions or CNS neoplasms, or have focal neurologic findings that include papilledema and depressed level of consciousness should have empirical antibiotic therapy started promptly, even prior to neuroimaging and LP. A significantly depressed level of consciousness, seizures, or focal deficits do not occur in viral meningitis. Failure of a patient with suspected viral meningitis to improve within 48 hours should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging, laboratory studies, and another LP.

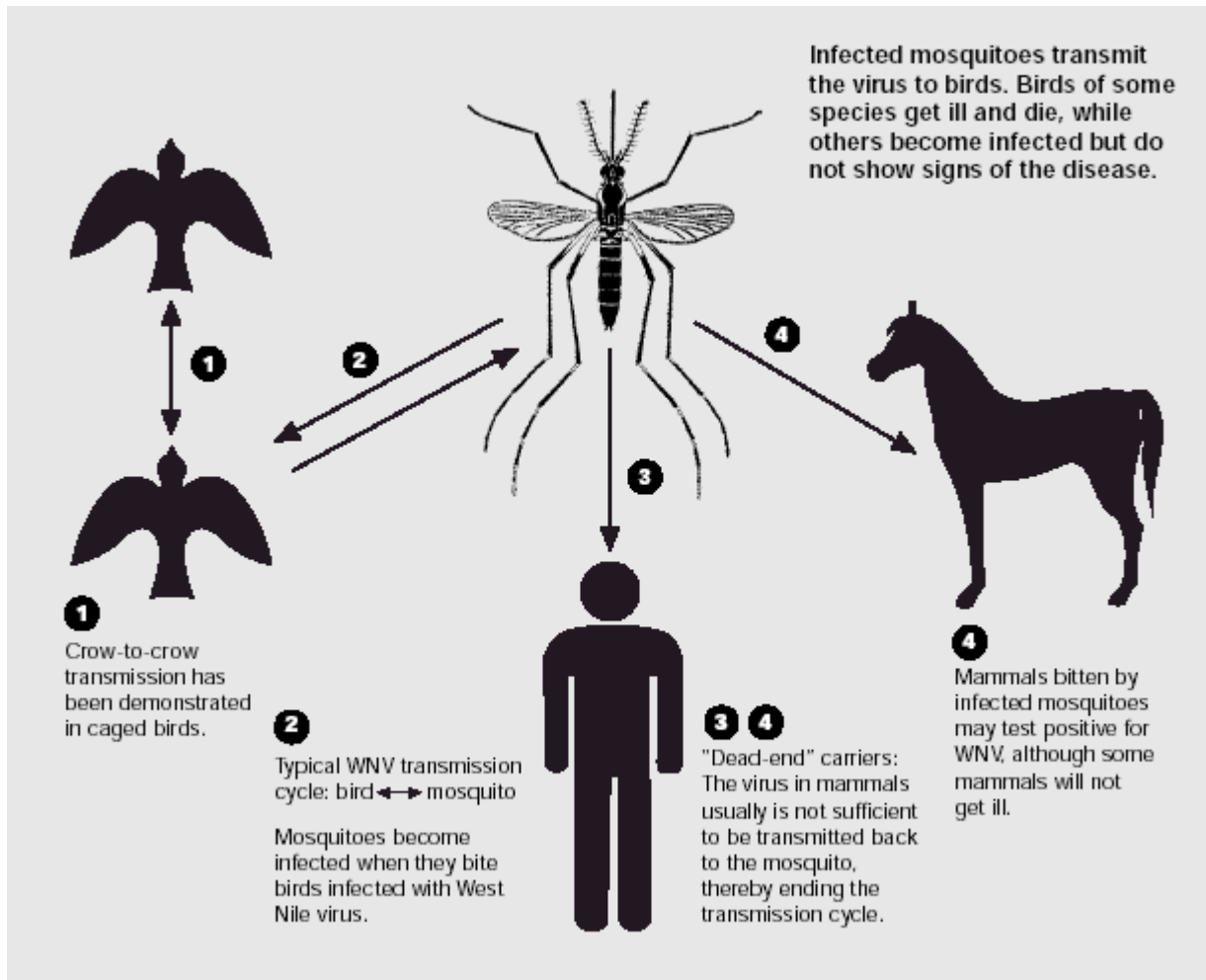
DISCUSSION:



*The image to the left is that of a Culex type mosquito and the image to the right is a flavivirus, more specifically the West Nile Virus.

West Nile Virus (WNV) is transmitted among wild birds by Culex mosquitos in Africa, the Middle East, southern Europe, and Asia. WNV was discovered in New York City in August 1999 and spread immediately to other areas of the Northeastern United States. WNV is a small, neurotropic RNA virus in the genus flavivirus. Other members of that genus also include Japanese encephalitis, St. Louis encephalitis, Rocio virus, and Murray Valley encephalitis virus. Again, wild birds are the major reservoir. Transmission occurs when a female mosquito feeds on a WNV-infected bird, the virus penetrates the gut, replicates, and invades salivary glands, where it is injected into new hosts during subsequent feedings. WNV infects the extraneural tissue of hosts first, produces viremia, and then invades the central nervous system. Humans, and multiple species of mammals, serve as incidental hosts because the viremia is neither sufficiently high nor prolonged enough for subsequent mosquito transmission.

The only human to human transmission documented is among organ transplantation or blood transfusion from infected donors, in utero, and through breast milk. Please see the figure below for more information on WNV transmission.



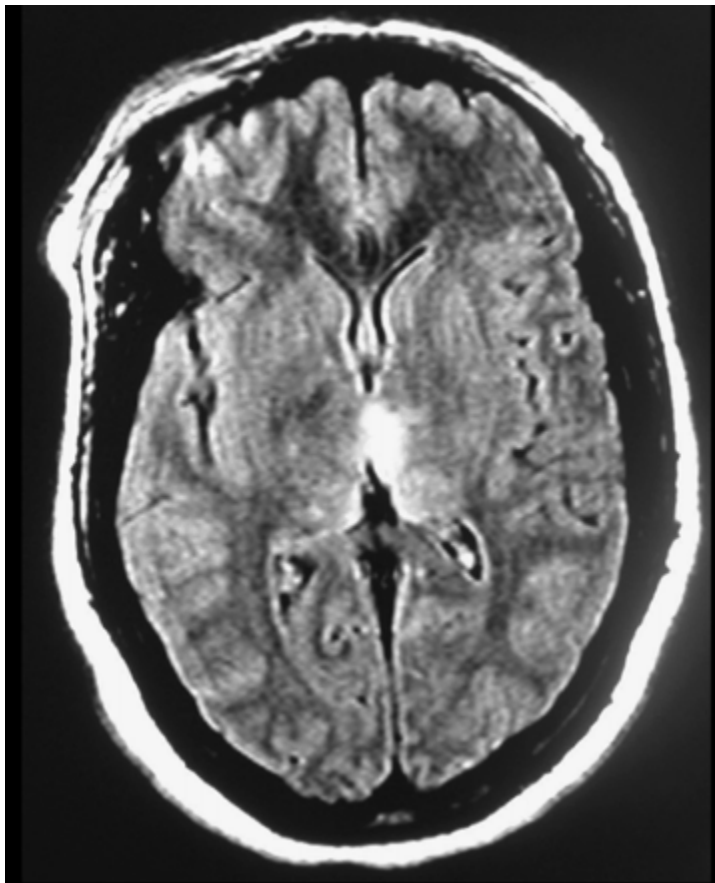
WNV is a common febrile disease, but rarely causes aseptic meningitis or encephalitis. Approximately 80% of all human WNV infections are asymptomatic, as evidenced by a 1999 study done in the New York City area in 1999 by routine screening of blood donors. Nearly 20% of those infected with WNV will develop fever, fatigue, and sometimes a macular rash. This illness has been named West Nile Virus Fever. Most individuals with this illness never seek medical care, so the true incidence may be underestimated. The remaining individuals, **less than 1%**, will develop neurologic illness consistent with meningitis or encephalitis. Aseptic meningitis is a result of viral infection of the meninges, whereas encephalitis is the result of viral infection of the brain parenchyma. The fatality rate of individuals who develop neurologic disease, termed West Nile Virus Meningoencephalitis (WNVME), is approximately 10-15%. Risk factors for mortality are advanced age, greater than 50 years old, and immunosuppression.

According to the CDC website, for the year 2010 (last update October 12, 2010), there have been a total of just 13 cases of reported neuroinvasive disease cases of WNV. A total of 429 cases have been reported across the entire United States. The most highly affected states include New York which

has had 81 cases, Arizona with 74 cases, and California with 42 cases this year. You can find an updated list by states by searching “West Nile Virus” on their website, www.cdc.gov.

The presenting symptoms of WNVME can include fever, headache, muscle weakness, altered mental status, and seizures. CSF examination typically shows modest lymphocytosis, normal glucose, and normal to mildly elevated protein concentrations. Motor weakness and parkinsonian movement disorders are common. Some less common presentations include acute flaccid paralysis, optic neuritis, and chorioretinitis as well as complications of vitritis, retinal artery occlusion, and intraretinal hemorrhages, and diabetes insipidus.

The diagnosis of WNV viremia is low due to the short duration of illness. The WNV specific IgM ELISA can detect antibodies in the CSF in 3-5 days or in the serum even earlier. The IgG usually appears about 5 days after the appearance of IgM antibodies. Infections with flaviviruses commonly manifests with gray matter abnormalities on MRI. Although all of the gray matter may be involved, the thalamus is the most frequent location of involvement. MRI findings may be delayed as well. If WNVME is considered with high suspicion, repeat MRI should be done in cases where initial MRI findings were normal. The following is an example of an MRI that has a left thalamic lesion due to WNV infection:



Currently, there is no specific treatment for WNV infection. Although some other flavivirus are being treated with Interferon-alpha, currently it is only being studied for WNV. Supportive care remains the treatment and despite good care, long-term neurologic sequelae such as persistent weakness, cognitive dysfunction, and parkinsonism have been reported. Preventing WNV transmission means protecting one’s self from mosquito bites. Mosquito repellants are currently the best remedy,

however, getting rid of mosquito breeding grounds has been shown to be the best preventer. Vaccines are currently being evaluated in clinical trials.

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