CLINICAL CASE OF THE MONTH

A 49-Year-Old Man with Fever, Headache and Leg Weakness

Jeffrey P. Cardinale, MD, PhD; Oliver O. Gentile; Laya M. Reddy; Trung N. Tran, MD; Joseph A. Avalos, MD; Fred A. Lopez, MD

A 49-year-old man with an unremarkable past medical history presented to an outside hospital with a five-day history of fever, left leg weakness, myalgia and headache. The patient reported that the illness started as a fever and sore throat and he was originally diagnosed with streptococcal pharyngitis and prescribed antibiotics. The day after his initial diagnosis, his fever had progressed to include a headache, myalgia, a rash on his upper torso and right shoulder and sudden-onset left leg weakness with preserved sensation. With progressively worsening symptoms, he eventually presented to a local emergency department (ED), five days after his symptoms first started. He was experiencing continued left leg weakness, an inability to ambulate, persistent fevers to 103ºF, muscle aches, an intense band-like headache and confusion. The patient denied neck stiffness, photophobia, loss of sensation or any additional muscle weakness. He denied any recent travel aside from work, any sick contacts, recent tick/insect bites, history of sexually transmitted diseases or contact with animals. He reported no history of illicit drug use as well as no recent weight loss, trauma or radiation exposure. The patient had approximately a 10-pack-year tobacco smoking history. For the last ten years he drank about a six-pack of beer daily while onshore (roughly two weeks out of every month). He works on an offshore oil platform. He was not taking any home medications besides his recently prescribed antibiotics. He lived alone at home in a moderately rural area of South Louisiana. His family history was non-contributory.

A computed tomography (CT) scan of the head without contrast was unremarkable. A CT scan of his spine revealed degenerative disk disease of his lumbar region. A lumbar puncture (LP) performed at the outside hospital showed clear cerebrospinal fluid (CSF) with 343/cu mm of white blood cells (WBC; normal range: 0-5/cc mm) and 18cu mm of red blood cells (RBC; normal range: 0/cu mm); the WBC differential was 17 percent segmented neutrophils (normal range: 0-6 percent), 68 percent lymphocytes (normal range: 40-80 percent) and 15 percent monocytes (normal range: 15-45 percent). The CSF glucose and protein levels were 65mg/dL (normal range: 40-70mg/dL) and 151mg/dL (normal range: 15-40mg/dL), respectively. Additional CSF was sent to an outside lab for further work-up, including an Enterovirus panel, Herpes Simplex virus (HSV) and West Nile Virus (WNV). The patient was then transferred to our hospital for additional work-up and management.

Upon transfer, the patient reported that his symptoms persisted. He denied photophobia, neck stiffness, numbness and tingling, difficulty breathing or incontinence. His presenting vital signs included a temperature of 98.3ºF, heart rate of 79 beats/minute, respiration of 18 breaths/minute, blood pressure of 117/64 mmHg and an oxygen saturation of 94 percent on room air. He appeared fatigued and he had a morbilliform rash on his upper right chest, shoulder and arm. He had normal strength, tone and reflexes of his upper extremities bilaterally and his right lower extremity. His left lower extremity revealed 2/5 strength in flexion and extension as well as hyporeflexia of the patella and ankle. The patient had full range of motion in his upper and lower extremities. The patient's neck was supple with full range of motion. His mini-mental status exam was remarkable only for disorientation to time. Initial labs showed a normal WBC of 8.86K/uL (normal range: 3.9-12.7K/uL), hemoglobin of 15.4g/dL (normal range: 14-18g/dL) and hematocrit of 43.8 percent (normal range: 40-54 percent) as well as a decreased platelet count of 89K/uL (normal range: 150-350K/uL). His complete metabolic panel and urinalysis were unremarkable. His CSF cultures from the outside hospital continued to show no growth. A chest x-ray revealed no acute cardiopulmonary changes. The patient was empirically started on intravenous acyclovir, ceftriaxone and vancomycin. Blood cultures were performed as were viral panels for cytomegalovirus, HSV, HIV, and arboviruses including St. Louis encephalitis, eastern equine encephalitis, western equine encephalitis, California encephalitis, and WNV. The patient initially declined a repeat lumbar puncture. A MRI of the brain and spine did not reveal any acute changes. Electroencephalogram, electromyogram, and nerve conduction studies were also non-diagnostic. Blood studies for WNV were negative on hospital day three. On the fourth day of hospitalization, repeat lumbar puncture was performed and CSF results revealed 160cu mm WBC (normal range: 0-5/cc mm) with a differential of 6 percent segmented neutrophils (normal range: 0-6 percent), 88 percent lymphocytes (normal range: 40-80 percent) and 6 percent monocytes (normal range: 15-45 percent) along with a glucose of 58mg/dL (normal range: 40-70mg/dL) and protein of 217mg/dL (normal range: 15-40mg/dL). Antibiotics were subsequently discontinued. The following day, the outside hospital reported a positive WNV-IgM antibody from the original CSF sample. Acyclovir was stopped. Physical therapy services completed a functional analysis of his capabilities and implemented a strength improvement regimen. His paralysis, which began in his left lower extremity, ultimately included his left upper extremity and the flexors of his right lower extremities. With additional time

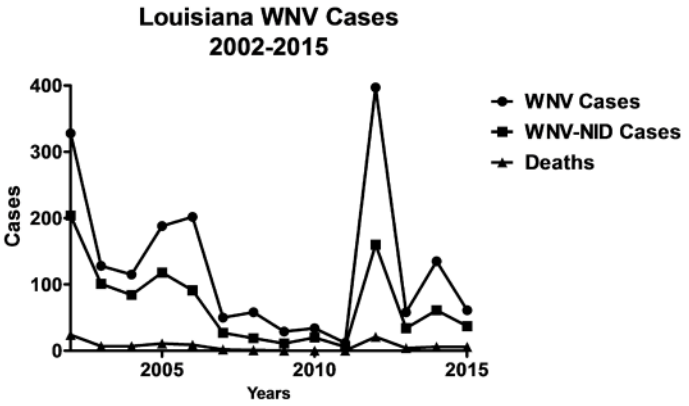


Figure 1. Reported WNV and WNV-NID cases and deaths due to WNV from 2002-Present (October, 2015) in Louisiana. Outbreaks occurred in 2002, 2006 and 2012. WNV: West Nile Virus; WNV-NID: WNV-neuroinvasive disease.

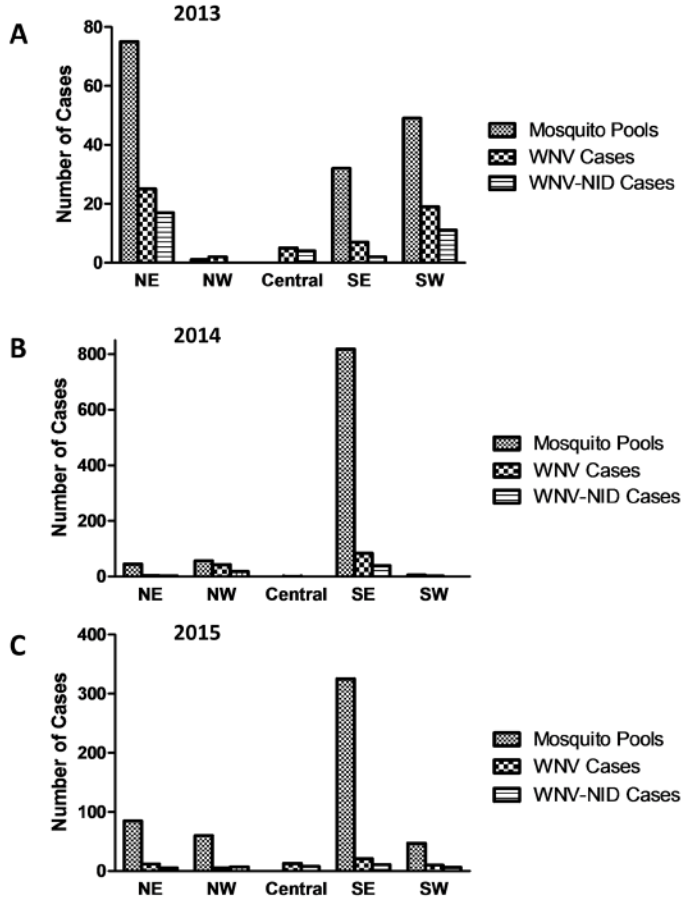


Figure 2. Louisiana state comparison of WNV positive mosquito pools versus human cases of WNV and WNV-NID in the various geographical regions of the state (See Map). Note that mosquito pool detection does not always correlate to WNV or WNV-NID cases. Furthermore, the region with the most pool and case numbers varies from year to year in no discernible pattern, though the SE region tends to have the most total number of cases. WNV: West Nile Virus; WNV-NID: WNV-neuroinvasive disease; NE: Northeast; NW: Northwest; SE: Southeast; SW: Southwest.

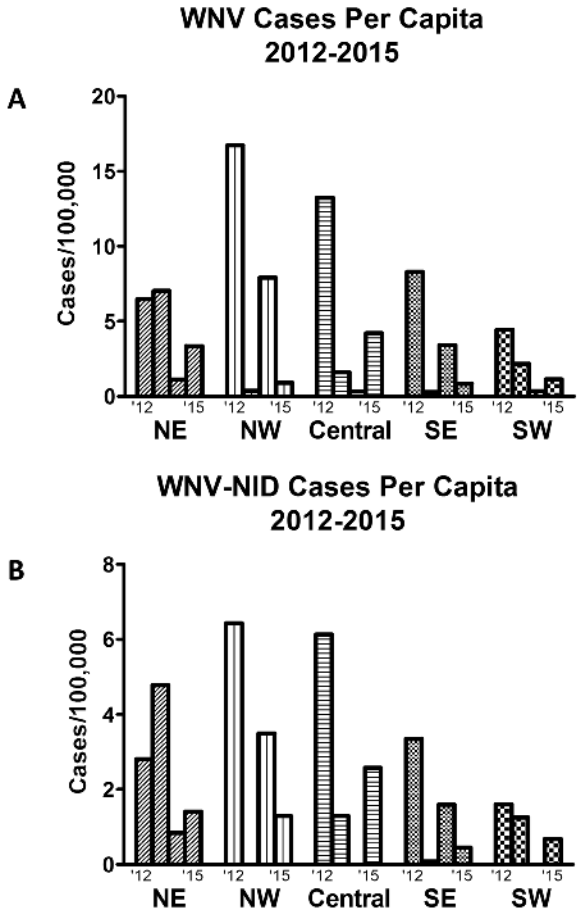


Figure 3. Comparison of WNV (A) and WNV-NID (B) cases per capita (cases/100,000 people) between years 2012-October, 2015 in the various geographical regions of the state (See Map). The SE region has the highest total population (2,446,864) but not always the highest number of cases per capita, whereas the least populated region, Central (309,761), had exceptionally elevated rates in 2012. While not conclusive, total population numbers do not seem to reflect an overall greater incidence, though the case raw numbers favor those more heavily populated areas. Population figures: NE: 355,761; NW: 544,249; Central: 309,761; SE: 2,446,864; SW: 877,450. Population statistics obtained from census.gov. WNV: West Nile Virus; WNV-NID: WNV-neuroinvasive disease; NE: Northeast; NW: Northwest; SE: Southeast; SW: Southwest.

and rehabilitation, his fatigue and general weakness improved and he regained full strength of his right lower extremity and left upper extremity, with partial recovery of his left lower extremity motor strength. The patient was transferred to an inpatient rehabilitation facility where he continues to improve, currently ambulating with a cane.

EPIDEMIOLOGY

West Nile virus, a member of the *Flaviridae* family, is one of the most widely dispersed arboviruses with a presence throughout Africa, Asia, Europe and the Americas, amongst others.[1] The virus was named for the West Nile territory of Uganda where it was originally found in a patient's blood sample in 1937.[2] It

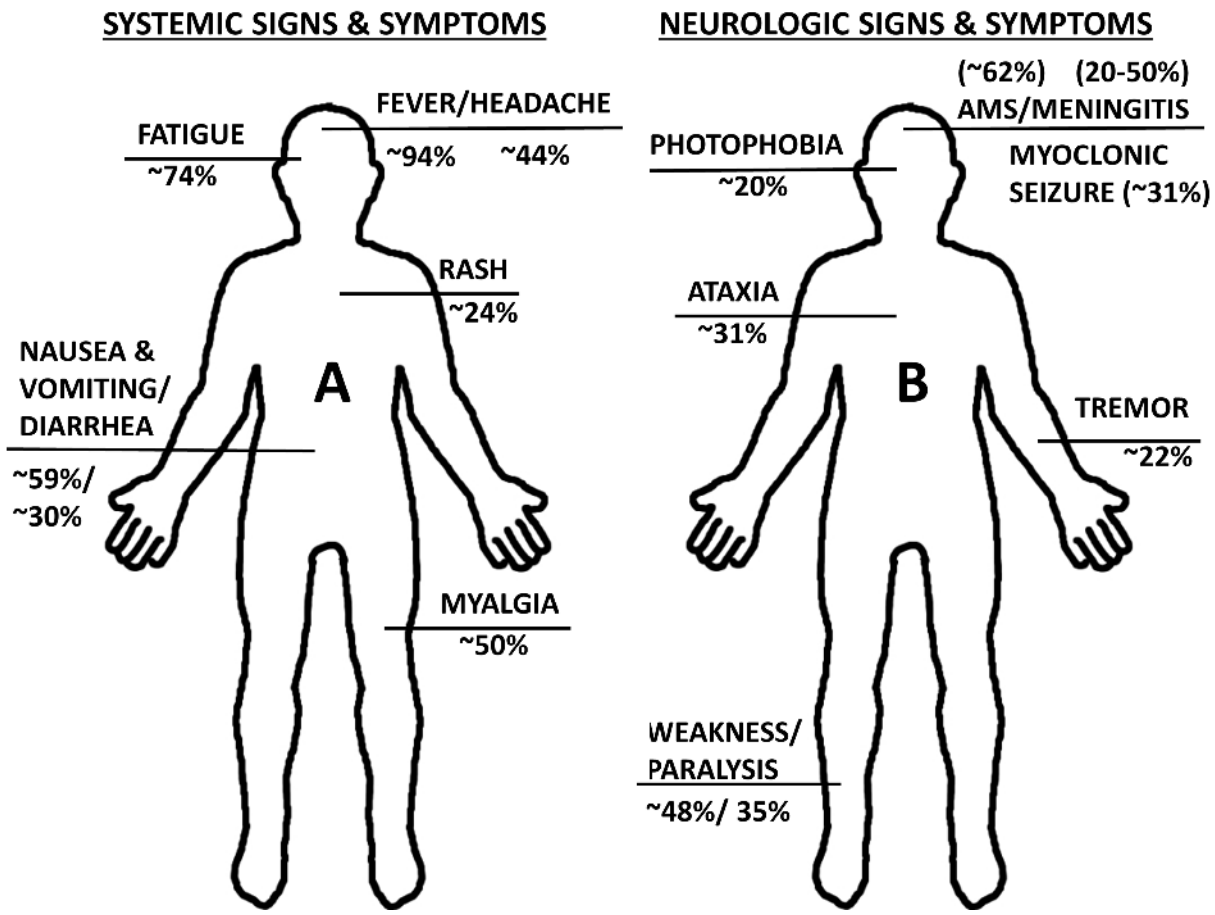
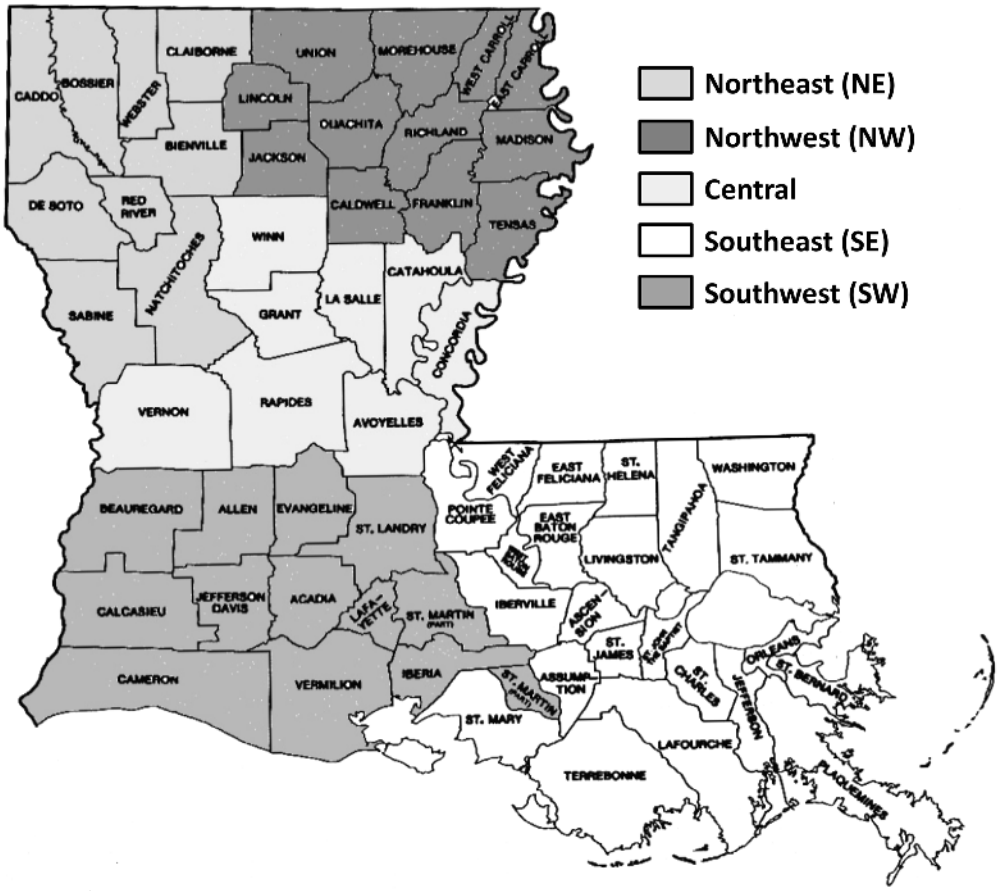


Figure 4. Prevalence of systemic (A) and neurologic (B) signs and symptoms of WNV.

was largely considered a minor risk for humans until an outbreak in Romania in 1996 followed by an outbreak in 1999 in New York.[1] It has since been detected in all 48 continental states including Louisiana, where the first reported case in 2001 involved a homeless man from Jefferson Parish.[3,4] The following year, 204 WNV-neuroinvasive disease (NID) cases were identified in patients from Louisiana ranging from two months to 94 years of age. Sporadic yet yearly cases continued to be detected in Louisiana until a major outbreak in 2012 in which 160 cases of WNV-NID and 21 deaths occurred (Figure 1).[5] The southeast region of Louisiana accounted for over 50 percent of the state's cases in 2012, but only 12 percent of the total in 2013, when the disease burden was more pronounced in northeast Louisiana.[5] Sampling mosquito pools remains the most effective means of WNV surveillance. Avian death tracking was a formerly used metric. However, Louisiana no longer recommends this methodology because the bird's death does not indicate when or where the infection first occurred.[5] Interestingly, when comparing 2013-2015 data, the use of mosquito pools to aid in determining areas of concern was not necessarily predictive of regions with the highest incidence of infected humans (Figure 2A-C).[5] For example, in 2014, the Southeast region had over thirteen times more WNV-positive mosquito pools detected over the next highest region, but less than half the number of total WNV human cases (Figure 2B). Moreover, the incidence of WNV and WNV-NID has fluctuated between the state's various regions without any obvious pattern, though the southeast region frequently has the most total numbers of cases (Figure 2A-C). In fact, when comparing per capita cases/100,000 population, even the more densely populated southeast region does not consistently demonstrate the highest disease prevalence of WNV and WNV-NID (Figure 3A and B).[5,6] While current modes of tracking are beneficial for post-exposure demographics, they fail to provide an accurate picture for determining when and where the cases will next present.[5,7]

Thus far in the United States through October 2015, WNV infections in humans, birds or mosquitos have been reported in 48 states (>1800 cases in humans). Of these human infections, 65 percent were classified as NID and 35 percent non-NID. This year (2015) in Louisiana, 517 WNV-infected mosquito pools have been detected. Compared to October 2014, 926 mosquito pools were found to be carrying WNV. Furthermore, this year 61 WNV human cases have been reported, with 37 cases of NID and five deaths. The 2015 WNV cases are distributed statewide, with southeast Louisiana accounting for 21 of the 61 reported cases.[5,7]

Over the past thirteen years in Louisiana, numbers have ranged from 6-204 cases of WNV-NID with the highest number report-



Map. Map of Louisiana and state parishes. The CDC divides the state into 9 regions based upon health and hospital administration zones. For simplification, these 9 regions were adjusted to represent the geographical areas of the state. The Northeast (NE) area represents the CDC's region 8. The Northwest (NW) area represents the CDC's region 7 while the Central area represents region 6. CDC regions 1-3 and 9 represent the Southeast (SE) area and regions 4-5 correspond to the Southwest (SW) area. The parishes within each geographical region are listed on the state map.

ed in 2002 (Figure 1). Temperature and rainfall, among other meteorological conditions, appear to play key roles in WNV trends. Transmission to humans appears consistently from the end of June to late September with the majority of cases occurring during the month of August. This period follows the natural amplification phase of the WNV transmission cycle when avian nesting and the initial rounds of avian and mosquito infection occurs.[5,7,8]

The cycle of transmission and stages of infection and replication of WNV are well understood. First, a mosquito vector, predominantly the Southern House Mosquito (*Culex quinquefasciatus*) in Louisiana, must consume a blood meal from a viremic bird.[3,9] The virus must infect the midgut epithelia and replicate there before being traveling hemo-lymphatically to the salivary glands of the mosquito. Once the viral load reaches sufficient levels in the salivary glands, the mosquito itself becomes a transmission vector when feeding on dead-end mammalian hosts such as horses or humans.[10]

Although mosquitos represent the primary vector for transmission of WNV, there are non-mosquito-associated transmission, including transmission through blood transfusion, organ transplantation, intrauterine transmission, breastfeeding and dialysis.[10,11] Risk factors for increased mortality with WNV infection include older age (>75 years), diabetes mellitus, immunosuppression, neuroimaging abnormalities, and the development of clinical symptoms such as limb weakness and altered mental status.[12]

PATHOPHYSIOLOGY

Much of our understanding of the pathophysiology of WNV is based on rodent models. In order to mitigate the host's hemostatic defenses against WNV, mosquitos inject combinations of vasodilators, coagulation inhibitors, platelet inhibitors, immunomodulatory, digestive, and antimicrobial proteins.[13,14] When a mosquito probes human skin with its proboscis, saliva is primarily injected extravascularly in the dermal layer, with the assistance of salivary endonucleases that facilitate entry through the collagenous medium.[15] WNV is first inoculated

peripherally by mosquitos and the initial stage of replication is believed to occur in Langerhans dendritic cells.[16] These specialized sampling cells of the immune system migrate to surrounding lymph nodes and eventually reach the spleen and kidney.[17] During this migration, there is a transient viremia that produces the flu-like symptoms classically associated with WNV infection. Approximately one week after infection, the virus is virtually absent from the serum and peripheral organs, with central nervous system (CNS) infection occurring in only a small subset of immunocompetent hosts. If CNS pathology develops, it can include infection and injury to the brainstem, hippocampus, and spinal cord neurons.[18-20]

There are several theories as to how WNV penetrates the blood-brain barrier: hematogenous spread, infection of the choroid plexus epithelial cells, infection of olfactory neurons, unwitting transport of virions by infected immune cells from the periphery to the CNS and retrograde axonal transport from the periphery to the CNS.[21,22] Other factors that contribute to CNS penetration include interferons and cytokines, such as TNF-α, which have been shown to increase endothelial cell permeability.[18,23]

As a neurotropic arbovirus in the *Flaviridae* family, WNV contains a single-stranded, positive sense RNA strand measuring approximately 11-kb without a polyadenylated 3′ end within a spherical enveloped capsid.[24] The genome codes in an open reading frame for a single polyprotein that is cleaved post- and co-translationally by host and viral proteases into three structural proteins and seven non-structural proteins. The 5′-end codes for the structural proteins, which include a capsid protein that binds viral RNA, a pre-membrane (prM) protein that prevents premature viral fusion and an envelope protein that mediates viral attachment, membrane fusion, and viral assembly.[25] The nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A NS4B, and NS5) are responsible for viral transcription, replication, and importantly, mitigation of host immune responses.[26]

Initial infection occurs through the binding of WNV to several cell surface receptors, including mannose-receptor, glycosaminoglycans, and DC-SIGN.[27-29] WNV gains entry into cells via receptor-mediated endocytosis with a subsequent pH-dependent conformational change of the envelope protein within the acidified endosome that allows fusion of the viral and endosomal membranes and release of the nucleocapsid into the cytoplasm. The virus then relies on cellular endoplasmic reticula to produce a negative-stranded RNA template for production of positive-stranded RNA which is either packaged into new virions or used as an additional template for synthesis of viral proteins.[30] These discrete viral elements assemble in the endoplasmic reticulum which bud off to form immature particles with prM protein on their surface and are then transported to the Golgi network where the prM protein is cleaved to M protein. The now mature virion is exocytosed for infection of unaffected cells and primed for continued viral propagation.[31]

PRESENTATION AND DIAGNOSIS

The incubation period for developing WNV infection ranges from 2-4 days. However, approximately 70-80 percent of WNV infections are asymptomatic.[32] Most of the remaining infections are either WNV fever (20-30 percent) or WNV-NID (< 1 percent of all detected WNV cases).[33] WNV fever presents not unlike other viral illnesses commonly including fever, fatigue, headache, myalgia and gastrointestinal complications such as nausea, vomiting, diarrhea and loss of appetite (Figure 4A).[32,34,35] Other symptomatic complaints with WNV infection include back pain, weakness and a non-purulent erythematous maculopapular rash.[36] For those who develop WNV-NID, the neurological manifestations of encephalopathy, meningitis, encephalitis, paralysis, seizure or a mixed combination of these conditions usually occurs several days after initial systemic symptom onset (Figure 4B).[11,37] Up to 35 percent of patients with WNV-NID develop frank paralysis resembling a lower-motor neuron pattern including loss of tone and hyporeflexia/areflexia.[11] The paralysis is typically asymmetric and rapidly progressive involving proximal over distal musculature that can even affect sphincter and diaphragmatic functionality. Additional neurologic sequela can include Parkinsonian movement disorders of rigidity and bradykinesia, cerebellar dysfunction, tremors and rarely, seizures.[11,34,35]

Diagnosis of WNV-NID depends upon a combination of clinical symptoms and laboratory findings. Lumbar puncture reveals CSF with an elevated WBC (often lymphocyte dominant except for early in the first week of disease/symptom onset when a neutrophilic predominance is noted), elevated protein levels and a normal glucose.[8,34] Detection of WNV IgM antibodies with enzyme-linked immunosorbent assay (ELISA) is the gold standard for disease confirmation with a sensitivity of 95 percent and a specificity of 90 percent, especially when tested within the first 7-9 days of symptom onset.[11] The virus can be detected directly via real-time polymerase chain reaction (RT-PCR), but the sensitivity is almost half that of ELISA.[11,12] While a positive ELISA and symptomology can confirm a diagnosis, nerve conduction studies can be useful in helping rule out other causes of paralysis. Radiographic studies can also be of use. While CT scan has limited capabilities in detecting changes observed in WNV-NID, MRI has shown hyperintense signal abnormalities in the cerebral cortex, the subcortical white matter, the spinal cord or a combination of these sites on, T2 and FLAIR modalities in up to 30 percent of WNV-NID cases.[34,38] According to the Centers for Disease Control and Prevention (CDC), the established criteria for WNV confirmation includes specific viral, viral antigen or nucleic acid isolation from tissue, blood, CSF or other fluid. Confirmation with plaque reduction neutralization test (PNRT), a highly specific non-commercially available test used by the CDC for case verification, is also considered diagnostic.[39]

TREATMENT AND PROGNOSIS

Treatment of WNV infection is primarily supportive.[11,34] Bed rest, oral hydration and over-the-counter pain relievers can

be used to reduce fever and relieve some symptoms. In cases where individuals develop WNV-NID, patients often need to be hospitalized to receive aggressive supportive treatment, such as intravenous fluids and medications to control pain, nausea and vomiting.[40]

To date, few studies evaluating specific therapies for WNV infection have been completed. Uncontrolled studies and case reports using agents such as interferon and ribavirin have not been conclusive and should be cautiously interpreted due to lack of large controlled studies confirming these treatment modalities, as most have only showed efficacy in vitro, in animal models,, or are only of theoretical benefit.[41] Intravenous immunoglobulin (IVIG) has been more thoroughly evaluated in a few randomized and controlled studies, with one demonstrating improved survival in a lethal WNV infection mouse model with high-titer IVIG from WNV-infected soldiers; its efficacy in humans is yet to be determined.[42] The results from another recently completed multi-centered Canadian and US longitudinal study investigating IVIG are still unpublished.[33] To date, public health efforts have emphasized prevention, including community wide mosquito eradication programs.[11] Lifestyle modification including judicious outdoor exposure during peak season and use of mosquito protective clothing and spray (DEET containing products) are also encouraged.[11] A WNV equine vaccine has been developed for veterinary use, but a similar approach in humans has not yet been developed or approved.[43]

Full long term recovery is expected for uncomplicated WNV fever and non-NID cases. Mortality following WNV-NID ranges from 10 to 30 percent, representing less than 0.1 percent of all infected patients.[33,34] The primary cause of death includes respiratory failure or nosocomial complications and a quarter of patients with WNV-NID require care in an ICU care setting.[44] Up to 95 percent of WNV-infected patients progress to a normal functional recovery within one year of initial disease diagnosis.[35]

CONCLUSION

Since its arrival in Louisiana in 2001, WNV has continued to concern both physicians and patients alike with its potential for significant morbidity and mortality. Despite local, state, and national CDC surveillance programs, predicting the future distributive patterns of WNV remains challenging. Currently, broadening mosquito vector control programs are prioritized in reducing the incidence of this disease until more effective, targeted preventative and therapeutic treatment options are identified. Until that time, increased awareness, rapid identification, and symptomatic stabilization of WNV-infected individuals are paramount to in its management.

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Dr. Cardinale is a first-year House Officer in the Department of Anesthesiology at Ochsner Medical Center, New Orleans, LA. **O. Gentile** is a third-year medical student at Tulane University School of Medicine, New Orleans, LA. **L. Reddy** is a third-year medical student at the University of Queensland-Ochsner Clinical School, New Orleans, LA. **Dr. Tran** is a second-year House Officer in the Department of Internal Medicine at Ochsner Medical Center, New Orleans, LA. **Dr. Avalos** is Ochsner Core Faculty and a Staff member within the Department of Internal Medicine at Ochsner Medical Center, New Orleans, LA. **Dr. Lopez** is the Richard Vial Professor and Vice Chair in the Department of Medicine at LSU-Health Sciences Center in New Orleans, LA.